

Is liver biopsy necessary in the management of alcoholic hepatitis?

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Abstract

Acute alcoholic hepatitis (AAH) is characterised by deep jaundice in patients with a history of heavy alcohol use, which can progress to liver failure. A clinical diagnosis of AAH can be challenging to make in patients without a clear alcohol history or in the presence of risk factors for other causes of acute liver failure. Other causes of acute on chronic liver failure such as sepsis or variceal haemorrhage should be considered. Liver biopsy remains the only reliable method to make an accurate diagnosis. However, there is controversy surrounding the use of liver biopsy in patients with AAH because of the risks of performing a percutaneous biopsy and limitations in access to transjugular biopsy. We review the existing literature and find there are few studies directly comparing clinical and histological diagnosis of AAH. In the small number of studies that have been conducted the correlation between a clinical and histological diagnosis of AAH is poor. Due to this lack of agreement together with difficulties in accessing transjugular liver biopsy outside tertiary referral centres and research institutions, we cannot advocate universal biopsy for AAH but there remains a definite role for liver biopsy where there is clinical diagnostic doubt or dual pathology. It

also adds value in a clinical trial context to ensure a homogeneous trial population and to further our understanding of the disease pathology. Further prospective studies are required to determine whether non-invasive markers can be used to accurately diagnose AAH.

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Key words: Alcoholic hepatitis; Liver biopsy; Diagnosis; Prognosis; Transjugular liver biopsy

Core tip: Acute alcoholic hepatitis (AAH) is a clinical syndrome of jaundice and coagulopathy in a patient with a recent history of heavy alcohol consumption. Clinical diagnosis is challenging and transjugular liver biopsy remains the gold standard. Here we discuss the literature which demonstrates there is a lack of agreement between clinical and histological diagnosis. This, together with limited availability of transjugular liver biopsy makes it impossible to advocate universal biopsy in all suspected cases of AAH. We suggest further research is conducted to prospectively compare histological and clinical parameters and to develop a reliable and accurate non-invasive diagnostic tool.

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INTRODUCTION

Acute alcoholic hepatitis (AAH) is a severe manifestation of alcoholic liver disease and is associated with a high short term mortality of 35% if untreated^[1]. The clinical syndrome is characterised by a history of excessive alco-

hol consumption (> 80 g ethanol/d in males and > 60 g ethanol in females) and a recent onset of deep jaundice, which can lead to progressive liver failure. Symptoms are usually non-specific such as fatigue, weakness and anorexia but there is usually tender hepatomegaly and often fever, ascites and encephalopathy^[2,3]. These features can also be seen in many hazardous drinkers making AAH challenging to diagnose clinically. Histology remains the gold standard in diagnosing AAH with well described features of steatosis, hepatocyte injury and neutrophil infiltration^[4,5]. However, there are difficulties in access to transjugular liver biopsy and subsequent expert histopathology review limiting its utility.

Indeed, there is controversy over whether histology is essential in the diagnosis of AAH with the American Association for the Study of Liver Disease and European Association for the Study of the Liver offering different guidance^[6,7]. Here, we discuss the existing evidence regarding liver biopsy in the management of AAH.

DIFFERENTIAL DIAGNOSIS OF AAH

Obtaining an accurate alcohol history is notoriously difficult but especially so in patients with potential AAH who are often unable to provide an accurate history due to symptoms of encephalopathy or acute alcohol withdrawal. Where there is uncertainty regarding recent heavy alcohol consumption as much evidence as possible should be obtained from relatives and friends or failing that primary or secondary care records. In all situations it is important to consider the differential diagnosis of acute liver failure including acute viral hepatitis, autoimmune hepatitis, Wilson's disease and drug induced liver injury. These factors can also co-exist in patients with heavy alcohol consumption, most commonly hepatitis C infection, which has been reported as a co-factor in up to 25% in one cohort^[8]. Although clues to the diagnosis can be ascertained from the history and laboratory tests, in complex cases or where there is diagnostic doubt a liver biopsy often supplements the clinical information.

Studies which included histological diagnosis as an entry requirement have shown a variation in the prevalence of cirrhosis in patients with AAH from 65%-95%^[9,10]. Therefore a minority of patients may present with AAH without features of chronic liver disease making it important to exclude other causes of acute liver failure.

However, in patients with chronic liver disease the key challenge in making a diagnosis of AAH is in differentiating it from other causes of acute on chronic liver failure (ACLF).

ACUTE ON CHRONIC LIVER FAILURE

ACLF is an increasingly recognised entity which, although not formally defined, has been the subject of 2 recent consensus meetings^[11,12]. Both groups describe the condition as an acute deterioration in a patient with chronic liver disease associated with jaundice and coagulopathy^[12]

and high 3-mo mortality due to multiorgan failure^[11]. In patients with alcohol-related cirrhosis AAH can be the precipitating cause of ACLF but other precipitants must be excluded especially gastrointestinal haemorrhage and sepsis of any source.

A recently published large multicentre prospective observational study was conducted to help establish diagnostic criteria for ACLF among European patients^[13]. In 197 patients with alcohol-related liver disease (ALD) who met the criteria for ACLF, alcohol consumption within the preceding 3 mo was considered the precipitating event in 69 (35%) but because only small numbers underwent liver biopsy a histological diagnosis of alcoholic steatohepatitis (ASH) could not be made in these cases. The other commonest precipitants were bacterial infection and gastrointestinal haemorrhage.

Further information can be obtained from studies in patients with ACLF who underwent liver biopsy. In a series of 68 patients with acute decompensation of ALD 36 had a clinical diagnosis of AAH but only 18 of these (50%) had corresponding histological features of ASH, while a further 13 (19%) had histological ASH without clinical AAH^[14]. In a separate study of 54 ALD patients admitted to hospital with ACLF a precipitating cause could only be identified in 30 (56%): 13 due to alcohol, 12 sepsis and 5 variceal bleeds^[15].

These studies demonstrate that AAH is not always the cause of ACLF in patients with ALD; other causes of acute decompensation must be sought.

LIVER BIOPSY IN AAH PATIENTS

ASH, originally defined by an international consensus group, was described as the presence of steatosis, hepatocyte injury (ballooning and apoptosis) and polymorphonuclear infiltration^[5]. Additional features of Mallory-Denk bodies and intraparenchymal cholestasis are observed but not necessary for diagnosis^[16]. However, these characteristic changes of ASH can be seen in patients with ALD without the clinical syndrome of AAH or even active alcohol consumption. As described above 13 out of 68 (19%) patients with acute decompensation of ALD had histological ASH without corresponding clinical AAH^[14]. ASH has also been noted in explant tissue from patients transplanted for ALD who were presumed to be abstinent. In 1 study ASH was noted in 32 of 148 (22%) explants from ALD patients including 25 who declared abstinence from alcohol for more than 6 mo^[17]. A Spanish group reported 36 out of 68 (53%) explants from ALD patients had ASH, which was not associated with a reduced survival^[18]. Therefore, it is important to be clear about terminology: we recommend the use of ASH to apply to the histological diagnosis while AAH should refer to the clinical syndrome.

In patients with severe AAH, many with deranged coagulation and significant ascites, the risks of performing a percutaneous liver biopsy are increased and a transjugular route is required. This is a well described and safe to per-

form procedure^[19] which should be considered standard practice in hepatology centres^[20]. In a systematic review of over 7500 transjugular liver biopsies minor bleeding (not requiring blood transfusion) and major complications were similar to the percutaneous approach (6.5% and 0.6% respectively) and death was rare at 0.09%^[21]. No specific subgroup analysis was performed in those with coagulopathy as the indication but in 183 patients with congenital coagulopathy there was no mortality and the minor and major haemorrhagic complication rates were similar to the whole group (6% and 0.5% respectively). Sufficient biopsy material allowed a histological diagnosis to be made in 96.1% of samples with a median number of 2.7 passes^[21]. In 132 patients presenting with AAH transjugular biopsy allowed accurate histological interpretation in 100% of cases with a mean length of 19 mm of tissue^[22].

Unfortunately little attention has been paid to the timing of biopsy in AAH, which is usually unreported in clinical trials. Early biopsy, as is the practice of several liver centres (median time of 3 d in 1 centre)^[22], may be more sensitive in confirming the diagnosis of AAH. Further studies are required to establish the optimal timing of liver biopsy.

Interpreting a liver biopsy specimen requires appropriate expertise and experience with access to specialist histopathologists but there still remains interobserver error. In patients with severe AAH and background cirrhosis this error has been shown to be minimal in one study with a high degree of concordance between 2 histopathologists ($\kappa = 0.77$)^[23]. However, this was based in a specialist hepatology centre with expert liver pathologists and was lower in patients without cirrhosis ($\kappa = 0.65$).

Access to transjugular liver biopsy is variable and generally only available in tertiary referral centres and academic institutions. Transferring patients between centres only to obtain a liver biopsy is logistically challenging, may increase the risk to the patient and is associated with additional costs.

HISTOLOGICAL SCORES TO DETERMINE PROGNOSIS

There is evidence that some of the histological characteristics as well as liver expressed soluble factors, such as chemokines and interleukins, can be used to predict clinical outcome from AAH. This could assist clinical decision making and guide treatment choices. Steatosis < 20% is an independent predictor of poor outcome^[24] and polymorphonuclear cell infiltrate is associated with severity of AAH^[25] and is correlated with 1 year survival^[10]. Liver tissue interleukin-8, a potent neutrophil chemoattractant, correlates with neutrophil infiltration and biochemical markers of outcome^[26,27]. Intercellular adhesion molecule-1, a leukocyte adhesion molecule associated with T helper cell recruitment to sites of inflammation, is elevated in AAH versus fatty liver and its level correlates with histological hepatocellular damage^[28]. CXC family chemokine expression correlates with prognosis^[25]

and CCL2 is elevated in AAH^[29]. However, a histological scoring system combining these multiple parameters has not been developed and many of these individual predictors have not been validated nor are they routinely used outside a research setting. A histological severity score including K8/18 staining (a marker for hepatocyte ballooning) shows good accuracy for predicting 90-d survival but has not yet been validated in a second cohort^[14]. Only 1 validated AAH histology score has been published in abstract form, finding that fibrosis stage, polymorphonuclear infiltrate, cholestasis and the presence of megamitochondria predicted 90 d mortality^[30]. Further studies in this area are required to establish a reliable and reproducible histological scoring system that predicts clinical outcome.

USING CLINICAL SCORES TO DIAGNOSE AAH

An accurate non-invasive clinical test for AAH remains elusive. There are a host of different clinical scoring systems in the literature which have been developed to determine severity and likely benefit from glucocorticoid therapy (modified discriminant function^[31]), prognosis (Glasgow Alcoholic Hepatitis Score^[32]) or response to glucocorticoids (Lille score^[33]). Little work has been conducted to examine how accurate these clinical scores are by comparing them to histological data. An abstract describing a literature review of 39 randomized controlled trials (RCTs) in AAH (11 of which had histological ASH as an entry criteria) suggested that overall 84.5% had histological ASH but this could be enriched to 96% if a minimum bilirubin level of 80 $\mu\text{mol/L}$ was used^[34]. Another study (also published only as an abstract) found that 70% of patients with a clinical diagnosis of AAH with an MDF ≥ 32 had histological confirmation of ASH^[35]. Further work to prospectively compare clinical and histological diagnosis of AAH is needed and to establish whether non-invasive methods of diagnosing AAH can be used accurately. One such study is currently underway in a United Kingdom RCT (STOPAH; ISRCTN reference number: ISRCTN88782125), which intends to compare histological and clinical parameters as part of a secondary analysis. This pragmatic study, which aims to reflect everyday United Kingdom clinical practice, includes all patients with a clinical diagnosis of severe AAH (defined as recent onset jaundice with a bilirubin > 80 $\mu\text{mol/L}$ and heavy alcohol consumption within the last 2 mo of > 80 g/d in men and > 60 g/d in women with a discriminant function ≥ 32) without the requirement for a biopsy. Liver histology from the subgroup that has a biopsy as part of an institution's standard clinical care will be compared to clinical parameters using this robust clinical definition of AAH.

CONCLUSION

Whilst it is clear that liver biopsy remains the recommended gold standard to diagnose ASH^[6] and has the

potential to be used as a prognostic indicator, opinion remains divided on its practical clinical utility. Liver biopsy in this group of patients is as safe to obtain by the transjugular route and provides sufficient tissue to make a histological diagnosis compared to the percutaneous route. It is mandatory where there is diagnostic uncertainty and is useful where cirrhosis is not clinically suspected. However, the widespread clinical utility of liver biopsy is limited by the lack of provision of transjugular liver biopsy in non-specialist centres and cannot therefore be recommended to form part of routine practice outside these centres. In addition, the timely specialist interpretation that is essential to make the diagnosis of ASH is also generally restricted to specialist centres. Efforts need to be made to improve clinical diagnostic accuracy and studies are required to prospectively compare histological and clinical features in patients with AAH. There is the suggestion that accuracy can be improved by using a high cut-off of bilirubin $> 80 \mu\text{mol/L}$ ^[34] but this also requires prospective validation, which may be provided by the STOPAH clinical trial.

Liver biopsy in AAH plays an important role in a research context: it can improve the homogeneity of the study population and reduce the risk of type II error. It allows researchers to study the mechanisms of alcohol mediated liver damage and identify new targets for therapy. However, including only patients with histological ASH may not actually reflect the patient population we treat in everyday clinical practice but only a highly selected subgroup. Until a reliable non-invasive diagnostic method for the clinical syndrome of AAH has been developed and validated, clinical trials should continue to include patients defined by a robust clinical definition of AAH.

In summary, we recommend the clinical use of transjugular liver biopsy in patients with severe AAH only where there is irresolvable diagnostic uncertainty and as a research tool to further our understanding of the mechanisms and pathology of the disease.

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