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RAPID COMMUNICATION

Liver biopsy in a district general hospital: Changes over two decades

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Abstract

AIM: To study liver biopsy practice over two decades in a district general hospital in the United Kingdom.

METHODS: We identified all patients who had at least one liver biopsy between 1986 and 2006 from the databases of the radiology and gastroenterology departments. Subjects with incomplete clinical data were excluded from the study.

RESULTS: A total of 103 liver biopsies were performed. Clinical data was available for 88 patients, with 95 biopsies. Between 1986 and 1996, 18 (95%) out of the 19 liver biopsies performed were blind and 6 (33%) were for primary biliary cirrhosis. Between 1996 and 2006, 14 (18%) out of 76 biopsies were blind; and the indications were abnormal liver tests (33%), hepatitis C (12%) and targeted-biopsies (11%). Liver biopsies were unhelpful in 5 (5%) subjects. Pain was the most common complication of liver biopsy (5%). No biopsy-related mortality was reported. There was a trend towards more technical failures and complications with the blind biopsy technique.

CONCLUSION: Liver biopsies performed in small district hospitals are safe and useful for diagnostic and staging purposes. Abnormal liver tests, non-alcoholic fatty liver disease and targeted biopsies are increasingly common indications. Ultrasound-guided liver biopsies are now the preferred method and are associated with fewer complications.

Key words: Complication; District general; Indication; Liver biopsy; Non-alcoholic fatty liver

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INTRODUCTION

Since the first reported percutaneous liver biopsy in 1923, the liver biopsy has become widely used in the investigation of liver disease and is currently the gold standard for confirming the diagnosis and for staging of liver disease[1]. However, it remains an invasive procedure, with a mortality risk ranging between 0.01% and 0.17%[2]. Studies have shown that less than one-third of the biopsies altered the treatment[3]; hence biopsies should only be performed in patients who would benefit from this procedure.

Over the last few decades, there has been a significant improvement in diagnostic and imaging techniques, as well as in the drug therapy of liver disease[1]. These have led to changes in our management of liver diseases. At the same time, changes in socio-economic status and life-style, have resulted in increased prevalence of obesity[4,5] and rising incidence of non-insulin diabetes mellitus[6,7]. Non-alcoholic steatohepatitis (NASH), the hepatic manifestation of the metabolic syndrome or insulin-resistant state[8], is now one of the most common indications for liver transplantation in the USA[9]. Consequently, the indications for liver biopsies in the UK will be expected to evolve over time.

We reviewed all liver biopsies performed in a single district general hospital (DGH) in the UK over two decades. We examined the indications, findings and complications of liver biopsy and explored the changes in our practice over the last two decades.

MATERIALS AND METHODS

Patients

All patients who had a liver biopsy were identified from the databases of the radiology and gastroenterology departments. Relevant clinical and laboratory information was collected retrospectively. Patients whose clinical information was incomplete were excluded from the analysis.

Table 1 Patient demographics and clinical features

	Median values (range)	Normal values
Age (yr)	57 (25-86)	
Sex (F/M)	51:37	
Liver biochemistry		
ALT (U/L)	66.5 (11-1103)	10-31
Bilirubin (μmol/L)	13 (5-430)	1-17
GGT (U/L)	221 (20-1394)	0-50
ALP (U/L)	145 (44-994)	45-145
Platelets ($\times 10^9$/L)	239 (93-813)	150-500
Indications for biopsy:		
Acute hepatitis	5	
Chronic hepatitis/Chronic elevated liver tests/Staging of disease	75	
Abnormal imaging	8	
Disease follow-up	3	
Routes of biopsy:		
Blind	32 (3[1])	
USS guided	60 (1[1])	
TJB	2	
Laparoscopic	1	

ALT: Alanine aminotransferase; GGT: Gamma glutamyltransferase; ALP: Alkaline phosphatase; USS: Ultrasonography; TJB: Transjugular liver biopsy. [1]Failed.

Liver biopsy protocol

In the absence of any contraindications, liver biopsies were performed when clinically indicated, as determined by the supervising clinician. The clinician performing the biopsy obtained an informed consent.

A full blood count (FBC) and clotting profile were obtained one day prior to the biopsy to ensure that the platelet counts were > 80 000/mm^3 and the international normalized ratio (INR) was < 1.3[1,2,10]. Appropriate platelet and clotting factors were given as necessary. An abdominal ultrasound of the liver was performed within six months of biopsy to ensure that there were no anatomical variants, biliary dilatation or focal or cystic lesions that may require a targeted biopsy[1,11]. The presence of moderate to severe ascites was considered a contraindication to percutaneous biopsy[1]. If considered safe and feasible, patients with massive ascites underwent paracentesis until completely dry, prior to the liver biopsy.

All liver biopsies were performed either as a 'blind' procedure or under ultrasound (USS)-guidance, depending on the personal preference of the clinician or the availability of a radiologist. Patients were discharged after six hours if the procedure was uncomplicated, and if the patient was clinically stable and pain free. A transjugular liver biopsy (TJB) was performed in patients with contraindications to a percutaneous biopsy.

Liver biochemistry, serology and immunology

All patients had liver biochemistry (serum bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyltransferase (GGT)) taken at the time of the initial clinical assessment. The normal ranges of these tests were: INR, 1; platelets 150-500 $\times 10^9$/L; bilirubin, 1-17 μmol/L; ALT, 10-31 U/L; ALP, 45-145 U/L; GGT 0-50 U/L. Serum aspartate transaminase (AST) is not part of the routine liver panel at our centre. A liver screen comprising of immunological tests (anti-nuclear antibodies, anti-mitochondrial antibodies, anti-smooth muscle antibodies) for autoimmune diseases, serological tests for hepatitis B and C viruses (hepatitis B surface antigen, anti-hepatitis C antibodies) and serum levels for metabolic disease (ceruloplasmin, alpha-1 antitrypsin, ferritin) was performed in all patients with abnormal liver biochemistry or abnormal USS. Patients with elevated ferritin levels had additional blood samples taken for haemochromatosis gene (C282Y/H63D) mutation analysis.

Usefulness of liver biopsy

In the present study, the usefulness of a liver biopsy was determined qualitatively by a) the success in establishing the diagnosis and/or b) any change (s) in the management based on the results of the liver biopsy

RESULTS

Patient population

A total of 103 liver biopsies were obtained between 1986 and 2006. Clinical data was available on 88 patients who had 95 biopsies. The number of successful liver biopsies was 91; 88 had one biopsy, 7 (4 failed 1st attempt; 3 follow-up biopsies) had two biopsies, while none of the subjects had > 2 biopsies. The median age of the patients was 57 (range, 25-86) years; 51 patients were female. 5 patients had acute hepatitis and 8 patients had focal lesions in the liver on abdominal imaging. The remaining patients underwent staging biopsies or diagnostic biopsies for chronic hepatitis or chronic elevations in liver function tests.

Liver function tests, platelets and clotting profile

The median INR was 1 (range 0.9-1.6). All patients had platelet levels > 80 000/mm^3 (median 239; range 93-813). The median values of the liver tests were as follows: ALT 66.5 (range 11-1103) U/L, ALP 145 (range 44-994) U/L, GGT 221 (range 20-1394) U/L and bilirubin 13 (range 5-430) μmol/L (Table 1).

Liver biopsy

Between 1986 and 1996: Number of patients and approach used: Eighteen patients underwent 19 biopsies. One biopsy was USS-guided and 18 were 'blind' biopsies (94.7%). One patient needed a repeat biopsy because of inadequate sample (blind) at the first attempt. The median size of liver biopsies was 1.5 cm (range: 0.5-2.5) (Table 2).

Liver biopsy findings: One-third of biopsies were performed for primary biliary cirrhosis (PBC). Two patients had elevated serum ferritin levels but only one was homozygous for the C282Y haemochromatosis mutation. Liver biopsy of the second patient showed features of porphyria cutanea tarda that was confirmed on faecal and plasma porphyrin tests.

Between 1996 and 2006: Number of patients and approach used: A total of 70 patients underwent 76 liver

Table 2 Liver biopsies between 1986 and 1995

Number of successful liver biopsies	Diagnosis pre-biopsy	History	Abnormal liver tests	Viral serology	Autoimmune / Immunoglobulins	Imaging	Others	Final Diagnosis
6	PBC	Y	Y	N	Y	Normal	n/a	PBC
3	AIH	N	Y	N	Y	Normal	n/a	AIH: 3 (staging)
1	LKM hepatitis	N	Y	N	Y LKM + AMA	Spleen +	n/a	Possible overlap AIH/PBC
3	ALD	Y	Y	N	N	Normal/Spleen +	n/a	ALD: 3 (cirrhosis in 1)
3	Abnormal Liver tests	N	Y	N	N	Echogenic liver	Elevated ferritin	NAFLD (simple steatosis): 3
1	ALD/Iron overload	Y	Y	N	N	Normal	Elevated ferritin	Porphyria cutanea tarda (plasma porphyrin 618, faecal porphyrin +)
1	Iron overload	N	Y	N	N	Normal	Elevated ferritin and homozygous C282Y	Primary haemochromatosis

Total number of biopsies performed: 19; Failed biopsies: 1; Successful biopsies: 18. Y: Present; N: Negative or not present; n/a: Not applicable; PBC: Primary biliary cirrhosis; AIH: Autoimmune hepatitis; ALD: Alcoholic liver disease; NAFLD: Non-alcoholic fatty liver disease; LKM: Liver, kidney, microsomal antibody; AMA: Anti-mitochondrial antibody.

biopsies; 59 biopsies were USS-guided and 14 (18.4%) were 'blind' procedures. Two patients had contraindications to a percutaneous biopsy (one had large volume ascites with raised INR and one had elevated INR), and underwent TJB. Laparoscopic liver biopsy was performed in one patient during laparoscopy performed for abdominal pain. Three patients needed a second biopsy after a failed initial attempt (2 blind, 1 USS-guided) while a further 3 had follow-up biopsies. The median size of liver biopsies was 1.7 (range, 0.1-3) cm (Table 3).

Liver biopsy findings: One-third of the biopsies were performed for undiagnosed elevation in the liver function tests and 12% were for staging of hepatitis C infection. Out of 59 USS-guided biopsies, 8 were performed in patients with focal lesions seen on abdominal imaging. Seven out of eight patients were found to have metastatic lesions while one patient had macrovesicular steatosis.

Changes in indications and/or findings over two decades

Between 1996 and 2006, 26% of patients were diagnosed with non-alcoholic fatty liver disease (NAFLD) (including non-alcoholic steatohepatitis), compared with 16.7% between 1986 and 1995. In the last ten years, targeted biopsies were also more common (11%; Table 3) but only one patient underwent biopsy for PBC.

Usefulness of liver biopsy

Diagnosis: In patients with elevated liver function tests but non-specific liver screen, liver biopsy confirmed the diagnoses in 25 out of 27 patients. It provided histological confirmation of metastases in 7 patients and was useful in confirming the overlap syndrome (autoimmune hepatitis/PBC) in 3 patients. Non-specific features were seen in 5 patients (5%).

Staging disease and treatment: Biopsy findings were used to stage autoimmune hepatitis, haemochromatosis, hepatitis B, hepatitis C, alcoholic liver disease and NAFLD. Those with moderate to severe fibrosis and cirrhosis at liver histology were placed on six-monthly hepatocellular carcinoma USS screening programme and had an upper gastrointestinal endoscopy to assess the presence and size of varices. Six patients with NASH were followed on a regimen of exercise and dietary changes, with tight glycaemic and blood pressure control. Nine patients with hepatitis C infections were treated with pegylated interferon and ribavarin.

Complications: Five patients experienced severe pain, requiring hospital admission and treatment with opiates. One patient developed a sub-capsular haematoma (blind biopsy); one patient developed pneumothorax (blind biopsy) that was managed conservatively; and another patient had an intra-abdominal bleed during TJB, requiring admission to the intensive care unit. There was no biopsy-related mortality.

DISCUSSION

In the present study, we observed an increasing number of liver biopsies being performed for elevated liver function tests. NAFLD was the most common diagnosis (70%) in these patients. When all the biopsies were taken in account, NAFLD accounted for nearly 30% of biopsies in our study population. These findings are consistent with the results of previous studies[12-14], and likely reflect that an increasing proportion of our population suffers from obesity[15-18] and non-insulin dependent diabetes mellitus[19,20]. Although the diagnosis of NAFLD can often be made clinically in patients with a combination of elevated liver tests, negative liver screen, 'bright' liver on abdominal USS and the presence of metabolic risk factors such as hypertension, non-insulin dependent diabetes mellitus, hyperlipidaemia and obesity[16,21,22], the distinction between simple steatosis and steatohepatitis can only be made by liver biopsy[23,24]. This is important because simple steatosis is considered a benign condition, while steatohepatitis can progress to

Table 3 Liver biopsies between 1996 and 2006

Number of successful liver biopsies	Diagnosis pre-biopsy	History	Abnormal liver tests	Viral serology	Autoimmune/ Immunoglobulins	Imaging	Others	Final Diagnosis
24	Abnormal liver tests	Non-specific Abdominal pains in 2	Y	N	SMA in 1 IgG in 1	Normal/ Echogenic	n/a	Simple steatosis: 12 NASH: 4 Autoimmune (including overlap): 2 Drug-related: 2 Microhamartomas: 1 (laparoscopy) Non-specific: 2 Venous congestion: 1
6	NAFLD	Metabolic features present	Y	N	IgA elevated in 2	Echogenic 3	n/a	NASH: 1 Simple steatosis: 4 Normal: 1
3	Alcohol	Strong alcohol history	Y	N	Elevated IgG in 1 Autoimmune normal	Normal 2 Ascites 1	n/a	ALD: 1 (staging) ALD: 1 (diagnosis; transjugular) AIH: 1
6	Iron overload	N	Y in 2	N	N	Echogenic 3	Elevated Ferritin in all	C282Y/C282Y: 4 C282Y/H63D: 1 NAFLD (simple steatosis): 1
2	Alcohol/Iron overload?	Strong alcohol history	Y	N	Elevated IgA	Echogenic 2	Elevated Ferritin in 2	C282Y/H63D + alcohol features: 2
8	Liver lesions on imaging	N	Y in 2	N	N	Multiple lesions noted on US/CT	n/a	Lung primary: 3 GIST: 1 GI tract: 2 Pancreas: 1 NASH: 1
9	Hepatitis C	Y	Y	PCR positive	N	Normal	n/a	Hepatitis C (staging) Genotype 1:6 Genotype 3:3
1	Hepatitis B	Y	Normal	Y	N	Normal	n/a	Hepatitis B (staging)
1	PBC	N	Y	N	Elevated IgM AMA: 1: 640	Normal	n/a	PBC
8	AIH	N	Y	N	AIH: ANA + SMA in 3 Isolated SMA in 1 LKM + AMA in 1 Non-specific: Isolated SMA in 2 ANA only in 1	Normal (7); Splenomegaly in 1	n/a	AIH: 3 (staging) (transjugular in 1) AIH: 1 (diagnosis) Possible AIH/PBC overlap: 1 Non-specific: 3
2	Drug induced	Y	Y	N	Polyclonal increase in Ig	Normal	n/a	Drug-cholestasis: 1 NAFLD(simple steatosis): 1
3	Miscellaneous	Y	Y in PUO	N	N	Normal	n/a	PUO: 1 Methotrexate: 2 (staging)

Total number of biopsies: 76; Failed biopsies: 3; Number of successful biopsies: 73. Y: Present; N: negative or not present; n/a: Not applicable. PBC: Primary biliary cirrhosis; PUO: Pyrexia of unknown origin; AIH: Autoimmune hepatitis; ALD: Alcoholic liver disease; NAFLD: Non-alcoholic fatty liver disease. NASH: Non-alcoholic steatohepatitis; LKM: Liver, kidney, microsomal antibody; SMA: Smooth muscle antibody. ANA: Anti-nuclear antibody; AMA: Anti-mitochondrial antibody; IgG: Immunoglobulin G; IgA: Immunoglobulin A; IgM: Immunoglobulin M; US: Ultrasound; CT: Computed tomography.

cirrhosis[25]. Aggressive control of metabolic risk factors has been shown to improve the liver function tests and liver histology[26-31]. Although it is not feasible to biopsy all patients with possible NAFLD, this should be considered in patients who are older (over 40 years), obese or have non-insulin dependent diabetes[18,32].

With improvements in chemo-radiotherapy regimens, many patients with metastatic diseases are offered neo-

Table 4 Liver biopsies for acute hepatitis

Acute hepatitis	Pre-biopsy diagnosis	Final diagnosis
1	Cause unknown	Likely drug-induced; prednisolone started
2	Cause unknown	Mild steatohepatitis
3	Pyrexia of unknown origin	Tuberculosis excluded
4	Cause unknown	No specific features
5	Cause unknown	Microhamartomas with cholestatic hepatitis

adjuvant and adjuvant therapy. Hepatic resection for colorectal metastases limited to the liver, has become the standard of care[33,34]. Imaging guided biopsy of liver lesions is being performed increasingly to confirm metastases and to determine the primary tumor. By contrast, a liver biopsy is no longer necessary to make a diagnosis of PBC. A persistently elevated E2AMA strongly suggests PBC, even in asymptomatic patients[35]. Moreover, Cox-regression analyses have shown that the main prognostic marker in PBC is serum bilirubin[36]; thus indicating that the presence of fibrosis or cirrhosis in PBC is of limited prognostic use.

Liver biopsies are currently recommended in patients with chronic hepatitis C before treatment to stage and grade the disease[37,38]. Six patients with genotype 1 disease and three with genotype 3 disease received combination treatment with pegylated interferon and ribavarin. Since over 75% of patients infected with genotype 3 hepatitis C have a sustained virologic response after six months of combination treatment with pegylated interferon and ribavarin[39]; a liver biopsy may be unnecessary in some of these patients. In the future, non-invasive fibrosis markers are likely to play a bigger role in staging liver disease. We found that in patients with isolated autoantibodies or complex clinical and laboratory features, a liver biopsy was able to confirm the disease processes. For example, in a patient with excessive alcohol consumption who also had elevated immunoglobulin levels, liver biopsy indicated a diagnosis of autoimmune hepatitis instead of alcoholic hepatitis.

Liver biopsies from five patients showed non-specific features (5%). It has been suggested that for evaluation of diffuse liver disease, a core of at least 1.5cm is required[40] as it provides at least 6 to 8 portal tracts for adequate histological assessment. Although the median biopsy size in the study was 1.5 cm, many samples were inadequate, with the smallest recorded size being 0.1 cm. Three of these patients had biopsy fragments measuring less than 1cm in size, which may account for the non-specific findings. Liver biopsies are generally not required in patients with acute hepatitis[1]. We however, found it helpful in three patients (Table 4).

The most common complication of liver biopsy is abdominal discomfort. Hospitalization is needed in up to 3% of patients for pain and hypotension[41,42], but major complications are rare[43]. At our centre, five patients (5.6% of patients, 5.2% of biopsies) were admitted for severe pain while another patient developed clinically significant intraperitoneal bleed after a TJB and required intensive care treatment. Consistent with published reports[44,45], we found a trend towards greater technical failures and complications with the 'blind' biopsy technique. Three out of four patients who needed a second liver biopsy had their initial biopsies performed 'blind'; two other patients, one with a pneumothorax and the second with sub-capsular haematoma also had 'blind' biopsies. In the last decade, nearly 78% of all biopsies in our unit were USS-guided. This increase is likely to be related to the increasing availability and safety of USS-guided liver biopsy[46,47].

Although our study population was small, it is reflective of the current DGH practice in the UK. Post-liver transplant, protocol liver biopsies are performed at the tertiary transplant units, hence the absence such data in the present study.

In conclusion, our findings confirm that liver biopsies in the DGH are safe and useful in the evaluation and staging of liver diseases. USS-guided rather than 'blind' liver biopsies are likely to be the preferred technique by patients and clinicians. NAFLD rather than PBC or viral hepatitis, will increasingly constitute the majority share of the liver biopsy workload.

COMMENTS

Background

Liver biopsy is a widely used tool in the investigation of liver diseases. However, it is an invasive procedure and studies have shown that less than one-third of the biopsies actually alter the management of patients. A liver biopsy should therefore only be performed in those patients who would benefit from such a procedure. Over the last two decades, changes in the socio-economic status and life-style have led to alterations in disease profiles. There is an increasing burden of obesity, type Ⅱ diabetes mellitus and non-alcoholic steatohepatitis. Non-alcoholic steatohepatitis is now one of the most common causes of chronic liver disease and indications for liver transplantation in the USA. Concurrently, there have been rapid improvements in diagnostic and treatment options for patients with liver disease. With such changes, we expect that indications for liver biopsy will also evolve over time.

Research frontiers

Between 1986 and 1996, liver biopsies were performed mainly in patients with primary biliary cirrhosis as part of the staging process. With the development of reliable immunological markers designed to confirm the diagnosis, and prognostic markers to predict outcome of primary biliary cirrhosis, liver biopsy is no longer necessary. Between 1996 and 2006, the majority of biopsies (> 40%) were performed for raised liver function tests and hepatitis C staging. Non-alcoholic fatty liver disease was also found to be more common. In the present study, only 5% of biopsies showed non-specific features and were therefore unhelpful in patient management. The rest of the biopsies confirmed the diagnoses of the primary liver disease or the presence of metastasis. Patients with end-stage liver disease were placed on regular surveillance and those with treatable diseases were managed according to the treatment protocols. The complication rates after a liver biopsy in a district general hospital were found to be similar to the published rates. Between 5% and 6% of patients were admitted for severe pain. There was a trend towards increasing technical failures and complications with blind liver biopsy. In the last decade, ultrasound-guided biopsies were obtained more frequently than blind biopsies.

Innovations and breakthroughs

This study confirms that a liver biopsy is safe and useful in evaluating and staging of liver disease, even in district general hospitals. The risks from a biopsy remains small, but ultrasound-guided biopsies should be the preferred technique. In the future, non-alcoholic fatty liver disease will account for the vast share of the biopsy workload.

Applications

Useful for practicing clinicians in smaller hospitals as it confirms the safety and

utility of a liver biopsy. Ultrasound-guidance may be safer. Non-alcoholic fatty liver disease is increasingly common.

Peer review

This is a very nice review that describes the historical changes in liver biopsy methodology over the past 20 years. The data presented is clear and concise and has been described clearly in the text.

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