Original Research Article

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Liver biopsy in gall stone disease: a prospective study in patients undergoing cholecystectomy

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ABSTRACT

Background: Cholelithiasis has affected mankind since many centuries. It not only affects the biliary tree but also has adverse effects on the hepatic parenchyma, which can get further complicated due to infected bile. Early intervention in these cases not only retards the unwanted effects but also prevents irreversible damage to liver. Aim of study was to see the effect of gallstone disease on liver in patients of GSD (Cholelithiasis, Chronic cholecystitis, CBD Stones).

Methods: All patients being subjected for planned cholecystectomy were taken as subjects irrespective of age, sex and co-morbid conditions.

Results: 90 patients were included in study and they were evaluated for secondary histopathological changes in liver. Abnormal liver histology was seen in 40% of the cases, with portal tract inflammation being the commonest abnormality seen in 24.4% of patients followed by fatty change (17.8%), cholestasis (10%), lobular parenchymal infiltration (8.9%) and one (1.1%) patient had fibrosis. Choledocholithiasis was associated with a greater incidence of positive bile culture (60%) and greater incidence of abnormal liver histology (80%).

Conclusions: Gall stone disease cause significant changes in liver histology and these changes are more common in those patients having long duration of symptoms. In patients of choledocholithiasis incidence of infected bile and liver histology changes are more as compared to cholelithiasis with chronic cholecystitis.

Keywords: Cholelithiasis, Choledocholithiasis, Gall stone disease, Liver histology, Liver biopsy

INTRODUCTION

Cholelithiasis has affected mankind since many centuries. Archaeological excavation demonstrating the presence of gallstone in mummies of young Egyptian women proves the age-old existence of this disease.¹

This disorder, which constitutes a major burden on the community (prevalence 6%) is more common in females as compared to males (3:1) and in approximate 15% cases first degree relatives are affected.^{2,3}

The first successful cholecystectomy was performed in 1882 by Langenbuch in Germany. In the present time cholecystectomy remains the standard treatment of cholelithiasis despite the advent of gallstone dissolving drugs and extracorporeal lithotripsy.⁴

In patients of gallstone disease, cholangitis can develop which on long run can cause secondary changes in liver like fatty liver, fibrosis, secondary biliary cirrhosis, reactive hepatitis, nonspecific inflammatory changes etc.

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In patients of choledocholithiasis liver suffers more damage as compared to cholecystitis and cholelithiasis.

Graham in 1918 was the first one to realise that gallstone disease may also affect liver and hence needed evaluation.⁵ Pioneering and landmark work on this was done by Mateer and co-worker as reported in a series of articles published between 1942 and 1948.⁶ This work was followed by many others such as those of Keller and Smetema and Edlund and Zettergren who disagreed with Mateer that cholelithiasis and cholecystitis induce any significant histological liver damage.^{7,8} Others such as Dunlap and Dockerty, Savory, Carajannopoulous, Raven confirmed the findings of Mateer.⁹⁻¹²

Gallstone disease not only affects the biliary tree but also has adverse effects on the hepatic parenchyma, which can get further complicated due to infected bile. Early intervention in these cases not only retards the unwanted effects but also prevents irreversible damage to liver. This present study has been undertaken with a view to elicit information on status of liver consequent to gallstone disease in Indian patients.

METHODS

Study setting

This study was conducted in the Department of Surgery for one year at a tertiary care teaching hospital in Delhi. Prior clearance by the college ethical committee was obtained. Sample size was 90.

Inclusion criteria

All patients being subjected for planned cholecystectomy were taken as subjects irrespective of age, sex and comorbid conditions. Patients of CBD stones were also included, after following the existing protocol for CBD stone i.e., ERCP (endoscopic retrograde cholangiopancreatography) guided stone removal followed by routine cholecystectomy.

Exclusion criteria

- Recent history of medical Jaundice (<3 months)
- Patients on hepatotoxic drugs.
- Patients of portal hypertension
- Patients with hepatitis B or hepatitis C.
- Deranged coagulation profile.
- Patients with acute cholecystitis.
- Patients with fatty liver on USG.
- Patient not willing/giving consent.

Informed consent

Informed consent was taken during the workup in OPD, patients and relatives were told about the nature of study and procedure.

All patients underwent a detailed physical examination with special reference to the hepatobiliary system;

Lab investigations

- Haemoglobin
- Total and differential leukocyte counts
- Platelet count
- Kidney function tests
- Liver Function tests
- Prothrombin time and INR

Radiology

Ultrasound was the primary diagnostic modality in all patients.

Type of surgery

All the patients undergoing laparoscopic or open cholecystectomy were included in this study.

Technique of bile aspiration

Bile was aspirated from GB after proper identification of structures in both open and laparoscopic technique.

Technique of liver biopsy

In both open and laparoscopic technique after gall bladder aspiration cholecystectomy was done. After gall bladder was taken out haemostasis was achieved around gall bladder fossa. Undamaged portion of the liver edge was selected and held by atraumatic forceps, using a sharp scissors around 1cm of liver edge was taken out and sent for histopathological examination. Haemostasis was secured using electrocautery.

Specimens sent

- 1. Gall bladder for histopathological examination.
- 2. Liver edge for histopathological examination.
- 3. Bile aspirate for culture and sensitivity.

Statistical analysis

Normally distributed continuous variables were compared using the unpaired t-test, whereas the Mann-Whitney U test was used for those variables that were not normally distributed. Categorical variables were analysed using either the chi square test or Fisher's exact test. P<0.05 was considered statistically significant.

RESULTS

Total of 90 patients were included in the study, minimum age was 18 years, maximum age was 64, mean age was 38 and most frequent age group was 40-49 years (33%) (Table 1).

Table 1: Age distribution.

| Age groups (year) | No. of patients | Percentage |
|-------------------|-----------------|------------|
| <20 | 1 | 1.1 |
| 21-29 | 19 | 21.1 |
| 30 - 39 | 27 | 30.0 |
| 40 - 49 | 30 | 33.3 |
| 50 - 59 | 8 | 8.9 |
| >60 | 5 | 5.6 |
| Total | 90 | 100.0 |
| Mean±SD | 37.44±11.30 | |

Sex distribution

Out of 90 patients 78(86.7%) were females and 12 were males.

Symptom duration

All the patients were symptomatic; the patients with acute cholecystitis were excluded from the study. The duration of symptoms in months were asked and noted. The maximum duration was 48 months, minimum was 4 months and mean duration was 17 months (Table 2).

Table 2: Symptom duration.

| Duration of symptom (months) | No. of patients | Percentage |
|------------------------------|-----------------|------------|
| 0 - 6 | 10 | 11.1 |
| 7 - 12 | 38 | 42.2 |
| 13 - 24 | 23 | 25.6 |
| 25 - 36 | 13 | 14.4 |
| >36 | 6 | 6.7 |
| Total | 90 | 100.0 |
| Mean±SD | 16.74±11.6 | 6 |
| Range | 4 - 48 mont | hs |

Out of 90 patients 8 patients had given history of jaundice. Only patients who had jaundice due to gall stones were included in the study and patients who had medical jaundice were excluded from the study.

Out of 90 patients 4 were alcoholic but ultrasonography of these patients showed no pathology in liver and clinically no signs of liver cell failure were present, so these patients were included in the study. Alcoholic patients with fatty liver on ultrasound were excluded from the study.

Comorbidities

28 out of total 90 patients had some form of comorbid conditions like diabetes mellitus, hypertension and thyroid diseases. 7 patients had only hypertension, 5 patients had only diabetes mellitus, 8 patients had only thyroid disease, 4 patients had thyroid disease as well as diabetes mellitus, 2 patients had hypertension with

diabetes mellitus and 2 patients had all three comorbid conditions. In all the patients the comorbid condition was under control.

Clinical features

None of the patients had signs of acute inflammation at the time of admission for surgery; liver and gall bladder were not palpable in any of the patients.

3 out of 90 patients had icterus and all 3 had history of choledocholithiasis for which 2 of the patients underwent ERCP and CBD stone removal, one patient underwent CBD exploration at the time of cholecystectomy.

Laboratory investigations

Liver function test including bilirubin, SGOT, SGPT, alkaline phosphatase was done in all the patients. It was within normal range in all the patients except 5 patients of choledocholithiasis.

Pre-operation ultrasonography

All the 90 patients had evidence of chronic cholecystitis on USG. All the patients had stones in gall bladder. 11 out of 90 patients had single stone in gall bladder lumen, 79 patients had multiple stones in gall bladder.

Liver echo-pattern

On ultrasonography liver echo-pattern was normal in all the patients. Patients who had evidence of fatty liver, cirrhosis or any liver pathology on USG were excluded from the study.

Common bile duct on USG- During workup for surgery 5 out of 90 patients had stone in CBD. Before routine cholecystectomy 4 out of 5 patients were sent to another centre for ERCP and stone removal and stenting, 1 patient underwent CBD exploration at the time of cholecystectomy.

Liver histology

Liver biopsy was examined by light microscopy in all 90 patients. In 54 patients liver biopsy was absolutely normal but in 36 patients significant changes were present in liver histology.

In liver biopsy various histological features were noted and tabulated. Fatty change was present in 16 patients, cholestasis was found in 9 patients, lobular parenchymal infiltration in 8 patients, and portal tract infiltration in 22 patients and fibrosis in 1 patient.

Age and liver histology

An analysis of patients according to age in correlation with their histological findings were performed. Patients

were divided in two groups those having abnormal histology in liver and those having normal histology. Mean age of patients having abnormal liver histology was 37.4 years and for normal liver histology it was 42.69 years.

Around 89% of the patients with abnormal histology are in age group of 30-50 years. The 'p' value came out to be 0.001 which is statistically significant (Table 3).

Table 3: Correlation between liver histology and different age group.

| Age | Liver histology normal | | Liver histology abnormal | | P |
|-------------------|---------------------------|-------|-----------------------------|-------|-------|
| groups (years) | No. of patients | % | No. of patients | % | value |
| <20 | 1 | 1.9 | 0 | 0.0 | |
| 21-29 | 19 | 35.2 | 0 | 0.0 | |
| 30-39 | 13 | 24.1 | 14 | 38.9 | |
| 40-49 | 3 | 5.6 | 18 | 50.0 | 0.001 |
| 50-59 | 4 | 7.4 | 3 | 8.3 | |
| >60 | 4 | 7.4 | 1 | 2.8 | |
| Total | 54 | 100.0 | 36 | 100.0 | • |

Symptom duration and liver histology

Patients were analysed for the symptom duration as against the presence of any histological findings. The cases were evaluated as two groups those with and those without histological changes. Around 72% of the patients having abnormal histology had symptom duration between 7-24 months. When compared the symptom duration with liver histology 'p' value came out to be 0.014 which is statistically significant (Table 4).

Table 4: Symptom duration and liver histology.

| Symptom duration | Liver histology normal | | Liver histology abnormal | | P |
|---------------------|---------------------------|----------|-----------------------------|----------|-------|
| (month) | No. of patients | % | No. of patients | % | value |
| 0-6 | 10 | 18.5 | 0 | 0.0 | |
| 7-12 | 25 | 46.3 | 13 | 36.1 | |
| 13-24 | 10 | 18.5 | 13 | 36.1 | 0.014 |
| 25-36 | 5 | 9.3 | 8 | 22.2 | 0.014 |
| >36 | 4 | 7.4 | 2 | 5.6 | |
| Total | 54 | 100.0 | 36 | 100.0 | |
| Mean±SD | 14.50± 11 | .97 | 20.11±10 | .47 | 0.025 |

Comorbidities and liver histology

28 out of 90 patients had some form of comorbidity like hypertension, hypothyroidism and diabetes mellitus. Out of 28 patients with comorbidities 12 patients had histopathological changes in liver and 16 patients had no changes in liver biopsy. Patients were divided into 2 groups those having any comorbidity and those having no

comorbidity. When compared this liver histology changes the 'p' value came out to be 0.710 which is not significant.

Liver histology and number of stones

Out of 90 patients 79 had multiple stones in gall bladder and 11 patients had single stone in gall bladder lumen. When compared with liver histology the 'p' value came out to be 0.693 which is not significant.

Gall bladder aspirate and liver histology

Out of total 90 patients on aspiration of gall bladder in 80 patients it was bile, in 08 patients it was mucus and in 02 patients it was pus. This gall bladder aspirate was compared with liver histology. The 'p' value came out to be 0.791 which is not significant.

Choledocholithiasis and liver histology

4 out of 5 patients (80%) of choledocholithiasis had changes in liver biopsy. All 4 patients had portal tract infiltration and cholestasis.

DISCUSSION

All 90 patients of symptomatic cholelithiasis with a provisional diagnosis of chronic cholecystitis were included in the study. 5 of the patients had cholelithiasis with choledocholithiasis. In all the cases intraoperative bile aspiration from gall bladder and liver biopsy from right lobe of liver was taken.

Symptom duration correlated with liver histology

The criteria of symptom duration have been included in study in an attempt to see the effect of it on histology of liver. This was felt to be especially relevant to our patient population as a number of patients report to a medical institution only after a protracted period of illness. However, it must be kept in mind that the natural history of gall stones is such that the patients diagnosed to have asymptomatic cholelithiasis have a two percent chance per year of experiencing symptoms.¹³

Therefore, it is possible to have patients who are relatively asymptomatic and yet have long standing cholelithiasis. The findings in present study were compared to the other similar study (Table 5).

Table 5: Comparison of symptom duration with other study.

| Study | | Minimum duration | |
|-------------------------|------------|---------------------|-------------|
| Present study | 48 months | 4 months | 17 months |
| George RK ¹⁴ | 300 months | 1 month | 27.9 months |

The findings in present study reveal significant association between duration of symptoms and changes in liver histology (Table 4). The 'p' value obtained was 0.014 which is significant. Hence it can be said from present study that a positive correlation exists between duration and liver histology changes and more is the duration of symptoms higher are the chances of getting significant changes in liver biopsy. However other authors like George RK, Geraghty and Triger disagree with the fact that symptom duration has any correlation with liver histology changes. 14-16

In the present study apart from 5 patients having choledocholithiasis in rest of the 85 patients liver function test was normal and hence it can be said from this study that liver function tests cannot predict the changes in liver histology except in cases of choledocholithiasis.

The following other studies done in this field also concluded the same. George RK also said that liver function tests cannot predict liver histology changes exception being obstructive jaundice caused by common bile duct stone. He Triger et al have opined that biochemical investigations are not useful in predicting histological appearances apart from cases with jaundice at the time of surgery. He

Liver histopathology

In the present study among 90 patients, 54 patients had entirely normal liver on histology. 36 patients had various histological changes in liver (Table 3). The histological criteria used by us and relative percentage of various changes are noted as: fatty change (17.8%), cholestasis (10.0%), lobular parenchymal infiltration (8.9%), portal tract infiltration (24.4%), fibrosis (1.1%).

In portal tract infiltration and lobular parenchymal infiltration, the cells were mononuclear cells consisting mainly of lymphocytes and occasional plasma cells and few polymorphonuclear cells.

The criteria used by different authors over the years have been different in each study. Colp and Doubilet in their case of 40 pts of acute and chronic cholecystitis found infiltration of portal fields by lymphocytes but they concluded that in patients without jaundice there is no significant change in liver biopsy.¹⁷ Mateer et al evaluated the liver under the subgroups of hepatosis (reversible parenchymal changes such as vacuolation etc), minimal stromal changes of increased periportal fibrosis and slight mononuclear infiltrate.6 Biliary fibrosis was described as the finding of periportal fibrosis with dilatation of biliary ducts. Kozoll evaluated the slides of autopsy studies of liver in patients with cholelithiasis under the various criteria of chronic passive congestion, parenchymatous degeneration, fatty liver, portal cirrhosis, acute hepatitis, toxic hepatitis, biliary cirrhosis, cholangitis.18

Raven RW in his 77 patients of cholecystitis and cholelithiasis found changes in 47.4%, biliary cirrhosis in 5 patients, cholangiohepatitis in 3 patients, fatty changes in 13 patients and most common inflammatory cell infiltration of periportal tracts in 23 patients and like the present study he also found chiefly lymphocytes. ¹² He found periportal fibrosis in 10 patients which is quite high if we compare that with present study. Triger DR in his study of 57 patients found only 13 were normal. ¹⁶ The criteria he used were acute duct obstruction, minimal portal tract inflammation and moderate portal tract inflammation.

In a comparatively recent study by George RK the histological criteria he used were liver architecture, fatty change, cholestasis, portal tract infiltration, lobular parenchymal infiltration and regenerative activity. ¹⁴ Most common change he found was mild portal tract infiltration similar to the present study.

The incidence of histological changes in the liver in a normal population has not been evaluated in present study as we have not included a control group and have instead relied on historical controls. There have been some reports on this respect also. Mateer also took biopsies in patients with peptic ulcer disease and found only a 7% incidence of normal livers. 6 The distribution of other histological changes was also similar in both groups. Dunlap et al have conducted a similar study on upper abdominal conditions such as pancreatitis, peptic ulcer etc. the findings in their study was similar to those of Mateer, Michel et al, found an 83% incidence of hepatocellular histopathological abnormality in a random surgical population as against only 54% in patients with cholecystitis. 6,9,19 These reports indicate it is yet not possible to definitively comment whether cholecystitis is responsible for the histological changes seen or whether such features are common to all abdominal pathologies.

Choledocholithiasis and liver histology and bile culture

In the present study 5 patients had choledocholithiasis, 4 patients underwent endoscopic retrograde cholangiopancreatography and stone removal from common bile duct before they were taken up for cholecystectomy and one patient underwent CBD exploration at the same sitting with cholecystectomy. Significant liver histology changes were present in 4 (80%) patients and all the 4 patients had portal tract infiltration and cholestasis. Bile culture was infected in 3 (60%) patients and 'p' value for this was 0.003 which is statistically significant.

Similar studies on liver histology in choledocholithiasis showed a higher incidence of significant changes in patients of common bile duct stone. WR Flinn study showed 7 out 12 patients of choledocholithiasis had significant liver histology changes. Intrahepatic cholangitis was found mainly in patients of CBD

stone.^{20,21} In study of Geraghty 11 out 14 patients had significant liver changes.¹⁵

CONCLUSION

Gall stone disease cause significant changes in liver histology and these changes are more common in those patients having long duration of symptoms. Infected bile leads to more damage to liver as compared to noninfected bile. In patients of choledocholithiasis incidence of infected bile and liver histology changes are more as compared to cholelithiasis with chronic cholecystitis. Comorbidities do not affect changes in liver histology in gall stone disease significantly. Standard biochemical tests of liver function, clinical examination, history and ultrasound are poor predictors of microscopic liver abnormalities. It cannot be said that these liver histopathological findings are specific to gall stone disease or seen in all upper abdominal pathologies. On the basis of this study and the reviewed literature it is suggested that early cholecystectomy may be performed gall in stone disease to prevent secondary histopathological changes in liver.

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Institutional Ethics Committee

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