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Contrasting liver function test patterns in obstructive jaundice due to biliary structures and stones

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Summary

Background: Obstructive jaundice is believed to be characterized by abnormalities of alkaline phosphatase (ALP), rather than aspartate transaminase (AST).

Aim: To compare liver function tests (LFTs) in obstructive jaundice due to malignant strictures with those of jaundice due to gallstones.

Methods: LFTs were measured immediately before endoscopic retrograde cholangio-pancreatography (ERCP) in 207 jaundiced patients. Group 1 ($n=69$) had malignant strictures, group 2 ($n=97$) had common bile duct stone(s), and group 3 ($n=41$) appeared to have recently passed a stone. LFTs in groups 2 and 3 were also analysed at maximal liver enzyme derangement, maximum hyperbilirubinaemia and during acute pain episodes.

Results: Group 1 had higher median bilirubin, AST and ALP levels than groups 2 or 3 ($p < 0.001$). In group 1, median rise in ALP exceeded that in AST (4.3× normal upper limit (NUL) vs. 2.6× NUL, $p < 0.01$), but in groups 2 and 3, AST and ALP were similarly elevated (both ~2× NUL). At the time of maximum enzyme derangement in groups 2 and 3, median AST elevation (4.4× NUL, 185 IU/l) exceeded that for ALP (2.4× NUL, 276 U/l), ($p < 0.001$), and this was also true at peak hyperbilirubinaemia in these groups (AST 3.6× NUL, ALP 2.4× NUL, $p < 0.01$. Similarly, severe pain episodes in groups 2 and 3 were accompanied by greater elevations in bilirubin and AST, but not ALP, compared with levels at ERCP.

Discussion: The conventional wisdom that ALP rises more than AST in obstructive jaundice holds true where the jaundice is due to strictures, but in obstructive stone disease, the rise in AST may equal that in ALP, or even exceed it during maximum jaundice and during painful episodes. Clinicians should consider the possibility of extrahepatic biliary obstruction, even when AST is the predominantly elevated enzyme.

Introduction

During the investigation of jaundice, a useful initial step is to determine whether the jaundice is haemolytic, hepatocellular or cholestatic in aetiology. Haemolytic jaundice results from excessive red blood cell destruction; hepatocellular jaundice results from injury to the liver. In cholestatic jaundice, either bile synthesis by the liver is impaired (intrahepatic cholestasis) or bile fails to reach the intestine, due to physical obstruction of the biliary tract (extrahepatic cholestatic or obstructive jaundice).

The investigations used to identify type of jaundice include liver function tests (LFTs): serum concentrations of bilirubin, alanine transaminase (ALT) and/or aspartate aminotransferase (AST), and alkaline phosphatase (ALP).[1–3] The serum transaminases ALT and AST are sensitive indicators of hepatocellular damage;[4] high levels

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are present within hepatocytes, and plasma levels rise as hepatocyte membrane integrity is lost during hepatocellular injury. ALP is located in hepatic sinusoidal and biliary canalicular membranes, and its synthesis is increased in cholestatic disease.

Liver chemistry abnormalities are often classified into 'hepatocellular injury' and 'cholestatic' patterns, to simplify their interpretation. Rises in AST and ALT are found in acute or chronic viral hepatitis, autoimmune hepatitis, and genetic conditions such as haemachromatosis, α_1-antitrypsin deficiency and Wilson's disease. Milder transaminase elevations occur in alcohol-related liver injury, steatohepatitis and cirrhosis. In 'cholestatic' diseases, where bile flow is obstructed due to anatomic obstructions to bile duct flow (extrahepatic cholestasis) or impairment of bile synthesis by the hepatocytes (intrahepatic cholestasis), raised conjugated bilirubin levels are thought to be associated with a far greater elevation of ALP than of serum transaminases.[2,3,5,6]

During the management of patients with extrahepatic biliary obstruction we often encountered patients with extrahepatic obstructive jaundice who appeared to lack the typical 'cholestatic' LFT profile. In this study, we retrospectively examined LFTs in patients with obstructive jaundice undergoing endoscopic retrograde cholangio-pancreatography (ERCP). LFT profiles in patients diagnosed with obstructing common bile duct stone disease were compared with those in patients diagnosed with obstructing pancreato-biliary strictures.

Methods

The computerized database of ERCP records for the period June 2000–August 2003 at a district hospital was searched, to identify consecutive patients having ERCP for obstructive jaundice. Patients were included if the ERCP confirmed biliary obstruction, or if recent radiological imaging showed gallbladder stones and biliary obstruction, but the non-obstructed cholangiogram at ERCP, associated with a resolving clinical/biochemical picture, suggested recent passage of a common bile duct stone. ERCPs which were repeated to further treat known common bile duct stones or replace blocked biliary stents, and ERCPs done electively for recurrent acute pancreatitis, were excluded. Patients who had biliary obstruction at ERCP, but in whom alcohol excess or hepatotoxic drugs were felt to contribute to LFT derangement, were also excluded.

On the basis of ERCP findings, eligible obstructive jaundice patients were then divided into: group 1, patients with biliary strictures that were either presumed or confirmed to be malignant in nature; group 2, patients in whom common bile duct stones were evident at the time of ERCP; and group 3, patients in whom the presence of resolving jaundice with common bile duct dilatation and gallbladder stones were highly suggestive of recent passage of a calculus from the common bile duct.

LFT abnormalities were compared in the three groups as follows. For all patient groups, LFTs immediately before ERCP were compared. For all patients, the highest bilirubin at any point preceding ERCP was documented. For groups 2 and 3, LFTs were also noted when levels were most deranged during the illness: either (i) when either AST or ALP was at its highest multiple of the upper limit of the normal range; or (ii) when the bilirubin was at its highest. For patients with common bile duct stones and patients with presumed recent passage of a stone, the LFTs during a bout of severe biliary pain (severe enough to lead to emergency hospital admission) were compared with LFTs for the same patient at the time of ERCP. Pain episodes are often due to impaction of a stone in the distal common bile duct, or the passage of a stone through the ampulla of Vater into the duodenum.

At our hospital laboratory, the normal range for serum albumin is 35–50 g/l, and the upper limits of the normal range are 17 μmol/l for bilirubin, 42 IU/l for AST, and 115 IU/l for ALP. Our hospital does not routinely measure ALT or γ-GT as part of the LFT profile. In addition to the absolute levels of AST and ALP, the enzyme ratio was calculated by dividing the absolute level by the upper limit of its normal range (NUL), to allow relative comparisons of AST and ALP derangements to be made more readily. Where appropriate, data from groups 2 and 3 were combined.

Statistical analysis

The liver biochemical data were not normally distributed and are presented as medians (interquartile range, IQR). The Wilcoxon rank sum test (Mann-Whitney U test) was used to compare data between different patient groups. Paired Wilcoxon signed rank test was used to compare the differences within groups at times of painful jaundice and prior to ERCP. The χ^2 test with Yates's correction was used to compare discrete data.

Results

Overall, 207 patients (105 male) with obstructive jaundice were eligible for inclusion: 69 with

malignant strictures, 97 with stones in the common bile duct, and 41 who had recently passed a stone. Median (IQR) ages were 74 (67–82) years for patients with malignant strictures, 71 (51–82) years for patients with stones, and 67 (53–76) years for patients with presumed recent passage of stone(s). Of the 69 with malignant biliary strictures, 52 had distal strictures due to pancreatic carcinoma, ampullary carcinoma or distal cholangiocarcinoma, and 17 had proximal strictures involving the hepatic duct bifurcation due to hilar cholangiocarcinoma or metastatic involvement of hilar lymph nodes.

LFT patterns at ERCP

Table 1 shows details of LFTs immediately prior to ERCP. Patients with strictures (group 1) were more jaundiced ($p < 0.001$) and had lower serum albumin concentrations ($p < 0.001$), than patients in groups 2 and 3. Group 1 also had greater elevations of AST and ALP above the upper limit of normal, compared to groups 2 and 3. In group 1, the rise in ALP (median 4.3× NUL) was greater than that in AST (median 2.6× NUL) ($p < 0.01$). In contrast, in groups 2 and 3, the rises in AST were similar to those in ALP (both ~2× NUL).

Within group 1, patients with proximal strictures had a higher median (IQR) bilirubin level than those with distal biliary strictures: 380 (160–289) vs. 195 (141–329) μmol/l ($p < 0.0001$). There were no differences in AST and ALP between patients with proximal and distal biliary strictures.

Peak hyperbilirubinaemia

The median (IQR) highest bilirubin recorded at any time before ERCP in group 2 was 66 (40–120) μmol/l; the figure for group 3 was similar, at 92 (54–146) μmol/l (Figure 1). In contrast, the highest bilirubin recorded before ERCP in group 1 was much greater (274 (176–400) μmol/l) than in either stone group ($p < 0.001$).

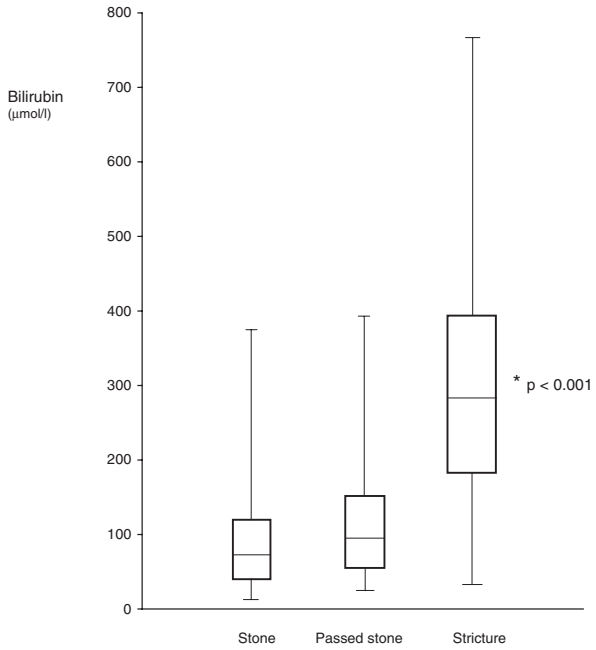

Figure 1. 'Box-whisker' plots of peak hyperbilirubinaemia in bile duct stone (group 2), passed stone (group 3) and biliary stricture (group 1) patients. Horizontal lines within boxes represent median values, box limits represent interquartile range and whiskers represent range. *$p < 0.001$ vs. stone and passed stone groups.

Maximally deranged LFTs in groups 2 and 3

(i) When AST ratio or ALP ratio was most abnormal

Of the 97 patients with common bile duct stones (group 2), the greatest AST or ALP derangement was in AST in 53 patients, and in ALP in 44. In contrast, in group 3 (presumed stone passage, $n = 41$) the greatest derangement was more often in AST levels ($n = 33$) than in ALP levels ($n = 8$) ($\chi^2 = 7.1$, $p < 0.01$). At times of maximal AST or ALP derangement, median AST rises were greater,

Table 1 LFT patterns in patients with biliary strictures (group 1), common bile duct stones (group 2) and recently passed stones (group 3) prior to ERCP

	Bilirubin (μmol/l)	Albumin (g/l)	AST (IU/l)	AST/NUL ratio	ALP (IU/l)	ALP/NUL ratio
Group 1 ($n = 69$)	256 (159–365)*	27 (23–31)*	111 (69–188)**	2.6 (1.6–4.5)**	490 (350–677)*	4.3 (3.0–5.9)*†
Group 2 ($n = 97$)	32 (17–68)	32 (27–37)	70 (35–122)	1.7 (0.8–2.8)	246 (142–392)	2.1 (1.2–3.4)
Group 3 ($n = 41$)	34 (20–73)	35 (32–39)	68 (31–123)	1.6 (0.7–2.9)	191 (138–284)	1.7 (1.2–2.5)

Values are medians (IQR). AST, aspartate aminotransferase; ALP, alkaline phosphatase; NUL, normal upper limit. *$p < 0.001$, stricture vs. stone groups. **$p < 0.01$, stricture vs. stone groups. †$p < 0.01$, ALP ratio vs. AST ratio for stricture group.

as a multiple of normal upper limit (NUL) than ALP rises (Table 2). For groups 2 and 3 combined, when either AST ratio or ALP ratio was maximal prior to ERCP, median AST level was 4.4× NUL (185 IU/l), whereas median ALP was 2.4× NUL (276 IU/l) ($p < 0.001$). At maximal AST or ALP derangement, median bilirubin was 62 μmol/l. In group 2 and 3 combined ($n = 138$), 12 patients had maximal AST levels >15× NUL (>630 IU/l) and the highest value recorded was 1096 IU/l.

(ii) When bilirubin was greatest

For groups 2 and 3 combined, when median maximal bilirubin was 77.5 μmol/l, median AST was more deranged than median ALP (3.6× NUL (151 IU/l) vs. 2.4× NUL (277 IU/l), $p < 0.01$) (Table 2). Consequently, the median (IQR) AST ratio/ALP ratio of 1.2 (0.6–2.5) was much greater than the AST ratio/ALP ratio prior to ERCP of 0.8 (0.5–1.2) ($p < 0.001$).

In group 2, when all LFT measurements prior to ERCP were scrutinized, the greatest bilirubin was associated with a greater derangement of AST in 45 patients and of ALP in 52 patients. In group 3, the greatest bilirubin was more likely to be associated with a greater derangement of AST ($n = 31$), than of ALP ($n = 10$) ($\chi^2 = 8.8$, $p < 0.01$).

LFT patterns of during severe pain episodes in groups 2 and 3

In groups 2 and 3 combined ($n = 138$), 93 patients had a bout of severe painful jaundice during their illness (Table 3). Compared to LFTs for the same patients at the time of ERCP, these severe

Table 2 Most deranged LFT patterns (greatest AST or ALP ratios and highest bilirubin) in stone (group 2) and passed stone (group 3) patients, with pre-ERCP LFTs shown for comparison

	Bilirubin (μmol/l)	AST (IU/l)	AST/NUL ratio	ALP (IU/l)	ALP/NUL ratio
At maximum AST/NUL or maximum ALP/NUL ratio					
Group 2 ($n = 97$)	57 (31–111)	171 (85–332)	4.1 (2.0–7.8)	290 (176–513)	2.5 (1.5–4.5)*
Group 3 ($n = 41$)	71 (50–117)	192 (114–362)	4.6 (2.7–8.6)	246 (153–428)	2.1 (1.3–3.7)*
Combined ($n = 138$)	62 (36–112)	185 (103–334)	4.4 (2.4–7.9)	276 (163–487)	2.4 (1.4–4.3)*
At highest bilirubin					
Group 2 ($n = 97$)	66 (40–120)	141 (71–268)	3.4 (1.6–6.2)	292 (185–480)	2.5 (1.7–4.3)**
Group 3 ($n = 41$)	92 (54–146)	174 (104–286)	4.1 (2.5–6.8)	247 (168–389)	2.1 (1.5–3.4)*
Combined ($n = 138$)	77.5 (41–130)	151 (78–274)	3.6 (1.9–6.5)	277 (172–450)	2.4 (1.5–3.9)*
Prior to ERCP					
Group 2 ($n = 97$)	32 (17–68)	70 (35–122)	1.7 (0.8–2.8)	246 (142–392)	2.1 (1.2–3.4)
Group 3 ($n = 41$)	34 (20–73)	68 (31–123)	1.6 (0.7–2.9)	191 (138–284)	1.7 (1.2–2.5)
Combined ($n = 138$)	33 (18–69)	69 (32–120)	1.6 (0.8–2.9)	224 (139–387)	1.9 (1.2–3.4)

AST, aspartate aminotransferase; ALP, alkaline phosphatase; NUL, normal upper limit. *$p < 0.01$. ALP/NUL vs. AST/NUL. **$p < 0.05$, ALP/NUL vs. AST/NUL.

Table 3 LFT patterns during severe pain episodes in stone (group 2) and passed stone (group 3) patients, compared with LFTs at time of ERCP

	Bilirubin (μmol/l)	AST (IU/l)	AST/NUL ratio	ALP (IU/l)	ALP/NUL ratio
During severe pain					
Group 2 ($n = 61$)	62 (32–104)	242 (90–368)	5.8 (2.1–8.8)	233 (148–359)	2.0 (1.3–3.1)
Group 3 ($n = 32$)	87.5 (51–122)	209 (137–335)	5.0 (3.3–8.0)	241.5 (169–433)	2.1 (1.5–3.8)
Combined ($n = 93$)	67 (41–108)	222 (114–362)	5.3 (2.7–8.6)	237 (53–386)	2.1 (1.3–3.4)
At ERCP					
Combined ($n = 93$)	31 (19–69)*	70 (32–136)*	1.7 (0.8–3.2)*	208 (127–335)	1.8 (1.1–2.9)

AST, aspartate aminotransferase; ALP, alkaline phosphatase; NUL, normal upper limit. *$p < 0.0001$, pain episode vs. time of ERCP, in combined stone and passed stone groups, paired signed rank test. Numbers are smaller than total group sizes ($n = 97$ and $n = 41$), because not all patients experienced a painful episode.

pain episodes were associated with increased levels of bilirubin (median 67 (IQR 41–108) vs. 31 (19–69) μmol/l, $p < 0.0001$), and AST (222 (114–362) vs. 70 (32–136) IU/l, $p < 0.0001$), but no change in ALP (Table 3). Expressed another way, the AST ratio/ALP ratio for the combined stone groups was 2.1 (1.1–4.8) during pain and 0.8 (0.5–1.2) prior to ERCP ($p < 0.0001$, paired Wilcoxon signed rank test).

Discussion

In this study, LFT patterns differed in obstructive jaundice due to biliary strictures and obstructive jaundice due to biliary stones. In general, by the time patients came to ERCP, those with biliary strictures had much higher bilirubin, AST and ALP concentrations than those with biliary stones. This may be because obstruction due to a stricture tends to be more complete and more prolonged, whereas obstruction due to a stone may fluctuate with stone movement. Furthermore, bilirubin (but not AST or ALP) was even higher in patients with proximal biliary strictures due to hilar cholangiocarcinoma or metastatic involvement of hilar lymph nodes, compared to patients with distal strictures due to distal cholangiocarcinomas, ampullary or pancreatic cancers.

It is often thought that ALP, not AST, is the predominantly deranged enzyme in obstructive jaundice.[3,5,6] At ERCP, this was true for our biliary stricture patients (median ALP 4.3× NUL, median AST 2.6× NUL). But in patients with obstructing biliary stone(s) or who had passed stones at the time of ERCP, AST derangement and ALP derangement were similar, both being approximately 2× NUL. This contrasts with studies that have focused on elevated ALP as being the main marker for common bile duct stones,[7,8] and standard medical texts that describe typical cholestatic liver enzyme profiles with common bile duct stones.[5,6]

Not only did the AST rise equal the ALP rise in groups 2 and 3 (stones and passed stones) at ERCP, but the AST rise often far exceeded the ALP rise when these patients had maximal hyperbilirubinaemia, maximum enzyme rise, or severe biliary pain.

Biliary pain in patients with common bile duct stones may originate from a common bile duct stone impacting in the distal common bile duct or passing from the common bile duct into the duodenum. Although our study cannot exclude the possibility that pain in such patients originates from an associated gallbladder stone impacting in the cystic duct, the observation that AST and bilirubin rose at times of pain suggests that the common bile duct stone obstructing the bile duct was responsible. Other studies have identified large rises in AST at the time of biliary pain due to calculous obstruction of the common bile duct.[9–12] Compared to group 2, who had common bile duct stones at ERCP, group 3, who had probably passed a stone, were more likely to have peak AST derangement as their maximal enzyme (AST or ALP) ratio, and to have worse derangements of AST (rather than ALP) at the time of maximal jaundice. These observations are consistent with the contention that passage of a stone through the ampulla into the duodenum is associated with a rise in AST.

Although AST was particularly elevated at the time of pain, ALP was not elevated above levels seen around the time of ERCP. Serum AST changes, arising from acute hepatocellular inflammation and necrosis, may be very fast to peak and subsequently fall after stones have disimpacted.[12] Serum ALP changes, dependent on altered rates of enzyme synthesis, tend to be far slower.

The results from this study challenge the common dogma[5,6] that bile duct obstruction due to stones will result in a typical cholestatic biochemical profile, with a greater rise in ALP than transaminases. AST rises were likely to equal or exceed ALP rises in our common bile duct stone patients. The possibility of extrahepatic biliary obstruction should not be overlooked when AST is the predominantly elevated enzyme. In particular, if pain is associated with a hepatitic pattern of LFTs, obstructing biliary stones should be suspected. Although pain associated with jaundice should always suggest gallstone disease, high AST levels at peak hyperbilirubinaemia without biliary pain may be misleading.[13] Clinicians may erroneously diagnose a hepatitic illness rather than a cholestatic illness, since grossly elevated AST levels tend to be typically associated with parenchymal liver disease.

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