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Reminder of important clinical lesson

Choledocholithiasis presenting with very high transaminase level

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Summary

We present three cases of choledocholithiasis presenting with a rise in transaminase to levels normally associated with acute hepatitis (alanine aminotransferase in excess of 1000 IU/l). All three cases had repeated investigation for liver disease before identification of common bile duct stones with magnetic resonance cholangiopancreatogram, and removal at endoscopic retrograde cholangiopancreatogram. We discuss the existing literature and the potential mechanisms of hepatocyte injury in extrahepatic obstruction.

BACKGROUND

Interpretation of deranged liver biochemistry classically involves categorising abnormalities into two patterns. A 'hepatitic' picture is characterised by a predominant rise in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). A 'biliary' picture is one in which there is a predominant rise in alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (GGT) released from biliary epithelium.[1] Marked rise in ALT (to greater than 1000 IU/l) is most commonly due to severe hepatocyte necrosis generally associated with viral or autoimmune hepatitis, ischaemia or drug toxicity.[2] The ALT is usually much lower in those presenting with acute biliary obstruction, but there are reports of transaminase elevation of >1000 IU/l in choledocholithiasis without underlying liver disease.[3–7] Appreciation of this under-recognised phenomenon in clinical practice may prevent unnecessary investigations and avoid delays in diagnosis.

CASE PRESENTATION

Case 1

A 75-year-old man was referred to the medical team by his general practitioner with a 24 h history of fever, abdominal pain, vomiting and cough. He had a background of one-and-a-half stone weight loss over 3 months and constipation for 2 months. His medical history included aortic valve replacement, coronary artery bypass graft, non-insulin-dependent diabetes and atrial fibrillation. He had no risk factors for acute viral hepatitis. He drank 6 units of alcohol per week. Medications on admission were metformin, simvastatin, aspirin, furosemide, atenolol and glycerine trinitrate. On admission, his temperature was 38.6°C, blood pressure, 125/62 mmHg, heart rate, 88 beats/min (bpm), and oxygen saturations were 94% on air. The abdomen was soft and non-tender and chest clear with a pan-systolic murmur. Five months later, he was referred from a general medical clinic to gastroenterology with persistently deranged liver function tests.

Case 2

A 63-year-old woman was admitted with a 24 h history of 'colicky' right upper quadrant pain associated with vomiting. She had a medical history of irritable bowel syndrome, hiatus hernia, labyrinthitis and depression. Medications on admission were lansoprazole, primeque (hormone replacement therapy), fluoxetine, prochlorperazine and orlistat. On examination, she was uncomfortable but afebrile and normotensive. The abdomen was soft with tenderness in the right upper quadrant, but no rebound or guarding.

Case 3

A 60-year-old woman with known gallstones and previous sphincterotomy was referred with a 24 h history of right upper quadrant pain identical to a previous episode of biliary colic. She had no other medical history and was not on any medications. On examination, she was apyrexial and normotensive, the abdomen was soft with tenderness in the right upper quadrant but no rebound or guarding.

INVESTIGATIONS

Case 1

Bloods on admission showed a white cell count (WBC) of 10 x 10^9/l, haemoglobin 11.9 g/dl, platelets 246 x 10^9/l, sodium 137 mmol/l, potassium 4.0 mmol/l, urea 8.2 mmol/l, creatinine 97 μmol/l, bilirubin 53 μmol/l, albumin 35 g/l, ALP 285 U/l, ALT 494 U/l, GGT 290 U/l, amylase 35 U/l and C reactive Protein (CRP) 99 mg/l. Hepatitis serology was negative. Blood cultures grew *Escherichia coli*. Bloods done at clinic 5 months later were AST 347 U/L, ALT 1067 U/l, GGT 267 U/l and bilirubin 70 μmol/l. Hepatitis A, B and C serology were again negative. He proceeded to have a MRCP that demonstrated a stone in the common bile duct (CBD).

Case 2

Blood tests on admission revealed haemoglobin 15.2 g/dl, WBC 18 x 10^9/l, platelets 298 x 10^9/l, bilirubin 33 μmol/l, ALT 680 U/l, ALP 156 U/l, GGT 237 U/l, amylase 39 U/l

and urea and electrolytes were normal. Abdominal ultrasound the following day demonstrated multiple calculi within a thickened gallbladder, intrahepatic and extrahepatic biliary dilatation and CBD measuring 15 mm. Liver function tests (LFT) deteriorated throughout admission; bilirublin 116 μmol/l, ALP 207 U/l, ALT 1136 U/l and GGT 237 U/l.

Case 3

Blood tests on admission revealed haemoglobin 15.2 g/dl, WBC 8.0 x 10^9/l, platelets 243 x 10^9/l, sodium 140 mmol/l, potassium 3.6 mmol/l, urea 4.8 mmol/l, creatinine 85 umol/l, amylase 44 U/l, bilirubin 44 μmol/l, ALP 61 U/l, ALT 621 U/l, GGT 239 U/l. Viral hepatitis serology was negative and repeated to confirm the result. Abdominal ultrasound demonstrated calculi in the gallbladder, a dilated CBD of 11.8 mm and prominent cystic duct and intrahepatic duct dilatation. LFT deteriorated while awaiting endoscopic retrograde cholangiopancreatogram (ERCP), with bilirubin 140 μmol/l, ALP 75 U/l, ALT 1101 U/l and GGT 274 U/l.

TREATMENT

Case 1

The patient was treated for cholangitis with *ceftriaxone* and *metronidazole* as an inpatient. Following MRCP, he subsequently underwent ERCP. The CBD stone was successfully removed by balloon catheter following sphincterotomy.

Case 2

She was treated for cholangitis with intravenous *Co-amoxiclav*.

Case 3

A single stone in the CBD was removed at ERCP after extending the previous sphincterotomy.

OUTCOME AND FOLLOW-UP

Case 1

After 6 days, the patient was discharged and an outpatient-flexible sigmoidoscopy and barium enema were arranged to investigate the recent altered bowel habit and weight loss. He was not referred for cholecystectomy.

Case 2

ERCP demonstrated diffuse dilatation of in the main biliary duct. Several CBD stones were identified, a 15mm stone was crushed with lithotriptor and the CBD was cleared with basket and balloon. LFT subsequently improved and the patient was discharged, later undergoing elective cholecystectomy.

Case 3

LFT settled after 6 days and the patient was discharged, later undergoing elective cholecystectomy.

DISCUSSION

Elevated transaminase levels of greater than 1000 IU/l are considered to be virtually diagnostic of hepatocyte necrosis due to viral or autoimmune hepatitis, ischaemia or drug toxicity.[2] Choledocholithiasis particularly in the context of an intact gallbladder is rarely recognised as a cause for such a phenomenon.

Our three cases demonstrate choledocholithiasis causing ALT rises in excess of 1000 IU/l and illustrate the importance of recognising such a phenomenon in order to prevent delayed diagnosis. Additional case series and experimental data support the observation that acute biliary obstruction can cause transaminase rises to greater than 1000 IU/l. Nathwani has reported an incidence of almost 10% at their centre but was unable to comment on associated factors,[2] and reports of transaminase levels of up to 2160 IU/l in choledocholisthiasis exist.[4]

In the 1960s, Aronsen demonstrated that CBD ligation in dogs resulted in transaminase rises into the thousands.[8] To our knowledge, there are five other series reporting elevated transaminases >1000 IU/l in calculous biliary disease.[3–7] Nathwani *et al* report 18 patients with such levels,[3] whereas only 3–5 patients have been reported in other series.[4–7] Additionally, elevations in transaminase levels >1000 IU/l have been reported in cholecystitis and pancreatic cancer.[9]

Histological findings in acute biliary obstruction demonstrate hepatocyte necrosis.[10] Transaminase elevations are more pronounced after morphine injection and extrahepatic biliary obstruction in animals post-cholecystectomy compared with controls [11 12] and it has been proposed that the gallbladder acts as a reservoir for sudden increases in pressure following ductal obstruction.[7] Older theories proposed by Mossberg and Ross included regurgitation of transaminases from biliary canaliculi into the bloodstream and increased enzyme production from damaged liver cells.[13] More recent research suggests that bile salt-induced hepatocyte necrosis is a consequence of mitochondrial dysfunction,[14] resulting in depleted ATP levels and sustained influx of Ca^{2+} leading to hepatocyte necrosis.[15]

Learning points

- Our three cases demonstrate choledocholithiasis can cause ALT rises in excess of 1000 IU/l and illustrate the importance of recognising such a phenomenon in order to facilitate early diagnosis and prevent unnecessary investigations.
- They reiterate the importance of interpreting liver function tests in the context of clinical history. Our third case had two sets of hepatitis serology sent, as the validity of the first result was questioned. Similar approaches have been taken in other centres, with patients being worked-up for liver disease and exocrine pancreatic disease, and isolated cases having liver biopsy.[3]
- Correct interpretation of a rise in transaminases is particularly important in patients postcholecystectomy, where bile duct stones are less common[16] and alanine aminotransferase in particular may be higher.[17]
- Transabdominal ultrasound has a limited sensitivity and MRCP, which has 90% sensitivity for detecting biliary stones, should be considered in cases of suspected CBD obstruction where no ductal calculi are noted on ultrasound.[18]
- Although the use of terms 'hepatitic' and 'cholestatic' to describe patterns of enzyme rise are of some value for teaching purposes, there is considerable overlap in the levels of enzyme rises and these terms must be used with caution.

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