'Non Surgical' jaundice- how to manage on the medical take

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Abstract

Malignancy and alcoholic hepatitis are cited as the most common causes of jaundice seen in secondary care. A patient with non-alcohol related jaundice, however, may require extensive investigations and early involvement of specialists. This article utilises a case presenting to the Acute Medical Unit, (AMU) to illustrate the importance of a careful and systematic assessment of non-alcoholic related jaundice.

Keywords

Jaundice, Bilirubin, Hepatitis

Learning Points

- Always look for clinical signs of chronic liver disease when assessing a patient with jaundice on the AMU.
- Systemic features of weight loss, anorexia may suggest chronicity of underlying condition e.g. malignancy or chronic liver disease.
- Pruritus, jaundice, pale stools and dark urine are common symptoms of patients with biliary obstruction.
- A disproportionate rise in ALT, compared to ALP, is seen in hepatocellular injury from various causes. However, a rise which is greater than 10 x upper limit of normal (ULN) is seen more commonly in acute hepatitis due to viruses, drugs and in hypoxic liver injury1.
- Deranged clotting (raised Prothrombin time or INR) is an important marker of hepatocyte dysfunction and can be present in jaundice secondary to both hepatocellular injury and obstruction.

Introduction

Jaundice is a term used to describe a state of hyperbilirubinaemia, which leads to a clinically detectable discolouration of the sclera, skin and mucous membranes, usually indicating the bilirubin is elevated to at least twice the upper limit of normal (ULN). Patients with new onset jaundice are commonly seen in the acute take and often, these patients are admitted under the medical team based on the suspected aetiology[2, 3].

Brief overview of bilirubin metabolism[4]

A brief knowledge of the metabolism of bilirubin is important in understanding the classification of jaundice and can be summarised as below.

Heme is derived from the breakdown of haemoglobin in the reticulo- endothelial system and is then further metabolised to bilirubin. Bilirubin, when initially formed, is in an unconjugated, water insoluble form. It is bound to albumin and transported to the liver for conjugation. In the liver, UDP- glucuronyl transferase conjugates bilirubin with glucuronic acid. This water soluble, conjugated bilirubin is then excreted in the bile and ultimately reaches the small intestine.

Most of the conjugated bilirubin is reabsorbed in the terminal ileum, and via entero-hepatic circulation, is transported back to the liver where it is utilised again. However, a small proportion if bilirubin reaches the colon where the bacteria metabolise it to form urobilin and stercobilin. These products give the natural colour to the urine and the stools.

Classification of hyperbilirubinemia

1. **Disorders of Bilirubin production (Pre hepatic)** – There is an increase in the presentation of unconjugated bilirubin to the liver, most commonly due to an increase in red blood cell breakdown i.e. haemolysis.
2. **Liver Disorders (Hepatic**) – Various toxic or disease processes reduce the ability of hepatocytes to metabolise or conjugate bilirubin. There is an increase in both unconjugated and conjugated proportions of total bilirubin in the blood.
3. **Obstructive (Post- hepatic) -** Any intrahepatic or extra hepatic obstruction to the flow of bile will result in the accumulation of primarily conjugated bilirubin.

The commonest causes of jaundice are summarised below (Table 1).

Analysis of bilirubin fractions (i.e. conjugated or unconjugated) allows further determination of the site of the injury (Table 2).

Case Vignette

A 58 year old male was referred by his GP, complaining of malaise and worsening jaundice over a two week period. He had no associated abdominal pain or fever, but had noted passing dark urine.

He had been treated for a chest infection with a course of co-amoxiclav 3 weeks ago.

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Table 1. Common causes of Jaundice

Pre Hepatic	Hepatic	Post Hepatic[5]
Haemolytic anaemias e.g. Hereditary spherocytosis, G6PD deficiency	Viral infections (hepatitis A, B, C and E)	Gall stones
Thalassemia	Chronic alcohol use (alcoholic hepatitis and cirrhosis)	Biliary Strictures including cholangiocarcinoma
Haemolysis due to drugs	Autoimmune disorders	Extra hepatic compression from cancers e.g. Cancer head of pancreas, lymphoma
Autoimmune haemolysis syndromes	Drugs	Mirrizi's syndrome
Mechanical heart valves	Pregnancy- Acute Fatty Liver	
Vascular grafts	Parenteral nutrition	
Resorbing haematomas	Infiltrative liver diseases e.g. Sarcoidosis, amyloidosis, malignancy	
Transfusion reaction	Congenital conjugated hyperbilirubinemia e.g. Dubin-Johnson syndrome, Rotor's syndrome	
	Congenital unconjugated hyperbilirubinemia e.g. Gilbert's syndrome and Crieglerr- Najjar's syndrome	
	Primary biliary cirrhosis / Primary sclerosing cholangitis	

He had a past medical history of hypertension, prostatism, and recurrent Urinary tract infections and his regular medications were ramipril, aspirin, bisoprolol and nitrofurantoin as prophylaxis for recurrent UTI's.

He did not consume alcohol and the family history was insignificant.

There were no stigmata of chronic liver disease although the patient was obviously jaundiced and had scratch marks on his body.

His blood tests, as done by the GP, showed a bilirubin of 134 µmol/L (<17), alanine transaminase (ALT) 234 IU/L (<50), alkaline phosphatase (ALP) of 342 IU/L (<140), INR 1.1, Albumin 35 g/L (>32), HB 13 g/L, PLTs 211x109/L and WCC 5x109 109/L.

What are the possible causes of his jaundice and deranged liver function tests?

This middle aged male presents with new onset jaundice and derangement of LFT's consistent with a mixed cholestatic and hepatitic picture.

The differentials at this stage are wide and include pre hepatic, hepatic and obstructive causes:

1. Drug induced liver disease (DILI)
2. Viral Hepatitis
3. Obstructive jaundice secondary to malignancy
4. Haemolysis/ Congenital Hyperbilirubinaemia

What further steps should be undertaken during his initial assessment?

Based on the differentials it is important to get liver profiles looking at intrinsic causes for hepatitis including a viral screen and initial imaging with an ultrasound examination should also be requested.

Is it pre-hepatic?

Haemolysis and Gilbert's syndrome classically present as isolated hyperbilirubinemia without any derangement of liver function tests, therefore making it highly unlikely to be responsible for the abnormal LFTs in our case. Pre hepatic causes can be excluded by looking at bilirubin fractions and requesting a haemolysis screen (increased serum lactate dehydrogenase, reticulocyte count, decreased serum haptoglobulin and a direct Coomb's test).

In general, a rise in serum bilirubin of less than three times the ULN and predominantly unconjugated (more than 70%), with liver function tests (LFT) otherwise normal is highly suggestive of Gilbert's syndrome.

If the serum bilirubin rise is greater than three times the upper limit of normal (ULN) with predominantly unconjugated (>70%) with normal LFTs, then haemolysis is more likely.

Table 2. Bilirubin fractions in Jaundice. Note: Eventually, unconjugated fraction goes up in all jaundice as the hepatocytes become saturated.

Test	Pre hepatic	Hepatic	Post hepatic
Total bilirubin (<21 µmol/L)	+	++	+++
Conjugated bilirubin (1-8 µmol/L)	Normal	Increased	Increased
Unconjugated bilirubin (<12 µmol/L)	Increased	Increased	Normal/ Increased

A serum bilirubin rise of greater than three times the ULN with predominantly conjugated (>50%) and abnormal LFTs, liver disease is likely[6].

Gilbert's syndrome[7,8,9,10]

This hereditary, chronic, mild unconjugated hyperbilirubinaemia affects 2-10% of the population. An inherited genetic defect inhibits the production of UDP–glucuronyl transferase, reducing the ability to conjugate bilirubin by 60–70%. This causes the serum level of unconjugated bilirubin to increase above the normal upper limit. Intermittent jaundice is the most common symptom and may be precipitated by dieting or fasting, surgery, dehydration, alcohol ingestion, use of certain drugs, infectious illnesses, heavy physical exertion and lack of sleep.

Additional diagnostic tests are rarely required, because a diagnosis of Gilbert syndrome can generally be made on the basis of the following findings:

- Unconjugated hyperbilirubinemia noted on several occasions
- Normal results from the FBC, reticulocyte count, and blood film
- Normal liver function test (LFT) results
- An absence of other disease processes

The most important reason to secure a diagnosis of Gilberts syndrome is to ensure a patient does not undergo further unnecessary investigation.

Case Vignette (continued)

The unconjugated bilirubin was 60 µmol/L, and conjugated bilirubin was 74 µmol/L, (normal range- Conjugated (direct) <8 µmol/L and Unconjugated (indirect) <12 µmol/L)

A haemolysis screen (serum lactate dehydrogenase, serum haptoglobulin, reticulocyte count and direct Coomb's test) in this case was negative, making either Gilberts or haemolysis extremely unlikely.

Having excluded pre hepatic causes, a non- invasive liver profile is mandatory to diagnose an intrinsic liver pathology. Given the exposure to antibiotics, a drug induced liver injury remains high on the list of differential diagnoses. A careful history should also be sought regarding any possible exposure to viruses that may cause an acute derangement in liver function tests, both liver specific (A, B and E) and more generic (EBV and CMV).

Drug induced liver injury (DILI)

DILI can be caused by a wide range of medications and is often classified as intrinsic (the drug is known to be hepatotoxic at higher dose e.g. paracetamol) or idiosyncratic (less common, affecting only susceptible individuals and is less related to dose)[11].

When assessing patients with suspected DILI, the history is of paramount importance. Care must be taken to ensure not only prescription medications are enquired about (i.e. such as exposure time, time until abnormal LFTs and presence of other liver disease) but also whether herbal or over the counter medicines have also been used. Drugs of misuse should be considered but one should also consider misuse of prescription medication such as anabolic steroids, especially in those with a predominantly cholestatic liver injury (Table 3).

With regard to our case, particular note should be made of the exposure to augmentin, prescribed in the community. Co-amoxiclav induced cholestatic liver injury is well reported in the literature and can often occur after cessation of the drug[12]. Nitrofurantoin is also associated with DILI, but tends to cause a more hepatitic picture, mimicking that seen in autoimmune hepatitis. Indeed, it can also trigger an autoimmune response with elevated immunoglobulin G and autoantibody positivity, but, as with autoimmune hepatitis, it may be responsive to steroids.

The vast majority of DILI will settle with time, but exclusion of others causes of liver disease is vital. Exclusion of the offending medications is the most important step in management of DILI and spontaneous normalisation of LFT's can be expected in most cases although the timescale for such improvement can be quite varied. Jaundice, if present can take several weeks to months to resolve. Supportive measures usually suffice, but pruritus may need to be treated with bile acid binding resins and/or antihistamines.

Worsening of LFTs should prompt early involvement of a specialist hepatology team. Several factors have been associated with poor outcomes and include ingestion of multiple drugs, concurrent alcohol consumption and worsening renal function[13]. Rarely, acute liver failure (characterized by hepatic encephalopathy and coagulopathy) can result from DILI, and requires discussion with a liver transplant centre.

Case vignette

Whilst the results of the non-invasive liver screen were awaited, he continued to feel unwell. Repeat LFTs revealed a worsening of his acute liver injury: ALT 689 IU/L, ALP 340 IU/L, Bilirubin 345 µmol/L, INR 1.2, and Albumin 32 g/L. An ultrasound was requested.

Could this be acute viral hepatitis?

A variety of viruses can cause a profound jaundice with a marked transaminitis, and can rarely lead to acute liver failure. Serological testing should be requested, as outlined in table 4. The ALT can often rise to > 1000 IU/L in an acute viral hepatitis, levels also seen in patients with DILI (especially acute paracetamol overdose) and ischaemic liver injury. Although alarming, such a high ALT is not prognostic, and the serum bilirubin and

Table 3. The table above lists some of the commonest agents responsible for DILI.

Drugs causing typically Hepatocellular pattern of liver injury	Drugs causing typically cholestatic pattern of liver injury	Mixed pattern
Isoniazid	Amoxycillin/ Clavulanate	Phenytoin
Co-trimoxazole*	Azathioprine+	Carbamazepine
Fluoroquinolones*	Anabolic steroidsAnabolic steroids Estrogens	Amiodarone
Macrolides*	Androgens and Estrogens	Sulfasalazine
Nitrofurantoin**	Cyclosporine	
Minocycline**	Glimiperide	
Valproate	Flucloxacillin	
NSAIDS		

*Can cause Cholestatic pattern of liver injury less frequently. **Can resemble Idiopathic Autoimmune hepatitis. +Can cause hepatocellular pattern of liver injury. (Adapted from Am J Gastroenterol advance online publication, 17 June 2014; doi: 10.1038/ajg.2014.131)

INR offer better information regarding mortality and the potential need for liver transplantation.

Liver specific viruses include hepatitis A, B (and D), C and E. Acute hepatitis B infection is most commonly transmitted sexually, and a thorough and forensic history is sometimes needed. However, in >95% of acute cases, it is self-limiting and does not progress to the more indolent chronic form. Although acute hepatitis C infection is possible, it usually asymptomatic in the vast majority of cases and so often goes undetected.

Hepatitis E infection is quite similar in presentation and clinical progression to hepatitis A infection. It has a faecal-oral mode of transmission and associated with poor hygiene and contaminated water. It has a rising prevalence in UK and is most commonly related to undercooked meat, usually pork[14,15].

It has an incubation period on average of around 40 days (15-60 days)[16]. Symptoms of hepatitis subsequently develop, with fever and nausea followed by abdominal pain, vomiting, anorexia, malaise, and hepatomegaly. Jaundice occurs in about 40% of patients and the ALT can rise dramatically with peaks of 1000-3000 IU/L reported[17].

It is usually self-limiting with full recovery and does not lead to chronic infection in immunocompetent patients. However, it has a worse prognosis in pregnant women and can cause fulminant liver failure in this subgroup. Immunocompromised patients can develop chronic hepatitis E and these patients may be considered for anti-viral treatment with ribavirin or pegylated interferon under specialist supervision[18]. Mortality has been reported at 1-3% rising to 15-25% in pregnancy.

Case Vignette (continued)

Viral serology was negative and repeat blood tests, showed a Bilirubin of 378 µmol/L (<17), ALT 678 IU/L (<50), ALP 401 IU/L (<140), INR 1.4, ALB 31 g/L (>32), WCC 9x109, PLTS 299x109, HB 12 g/L. An

Table 4. Commonly performed viral screen

Test	Interpretation	Action
Hepatitis B Surface antigen	Suggests exposure to HBV. Persistence beyond 6 months suggests chronic HBV infection.	Check other serological markers for HBV (HBe antigen, anti-HBc IgM, anti-HBc anti-HBs)
Hepatitis C Antibody	If positive, suggests HCV infection	HCV RNA testing and referral to hepatologist
Hepatitis A IgM	If positive, suggests acute hepatitis A infection. IgM may not be present in the serum until 10 days after onset of symptoms.	Spontaneous resolution in most cases. Inform local health authorities.
Epstein Barr Capsid IgM and IgG Antibody	Positive IgM antibody suggests an acute EBV infection (Infectious Mononucleosis-IM). IgG antibodies can persist for life.	Treatment for classical Infectious mononucleosis is supportive. Spontaneous normalisation of LFTs is expected.
Cytomegalovirus IgM	Positive IgM suggests acute CMV infection.	Immune competent patients may become symptomatic with IM like symptoms. Full spontaneous recovery is expected.
Hepatitis E antibody	Suggests infection. Hep E IgM antibody persists for 2 months.	Hep E PCR may be required for accurate diagnosis of active Hep E infection.

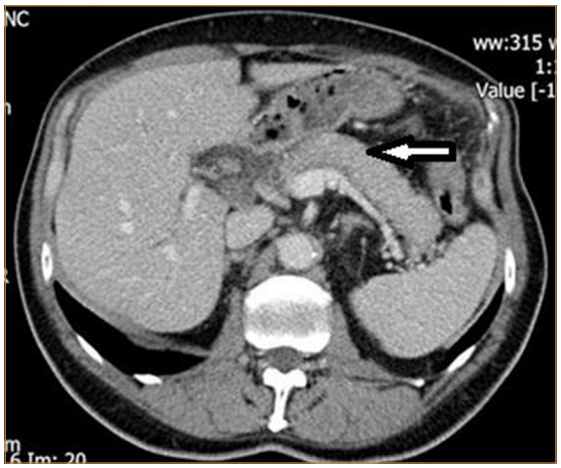

Fig 1. CT scan image with "Sausage shaped pancreas" (arrow)

ultrasound (USS) of his liver revealed prominent intrahepatic ducts and a thickened Common Bile Duct (CBD) of 7mm. The pancreas was not visualised very well. The patient remained afebrile.

The ultrasound suggests possible obstruction, given the prominence of the intrahepatic ducts and abnormality of the bile duct. However, in the absence of infection (note the normal white cell count and lack of pyrexia), the marked transaminitis remains unexplained, as it is not a typical finding of biliary obstruction.

The differential diagnosis of biliary obstruction include

1. Malignancy causing biliary obstruction
2. Choledocholithiasis
3. Obstruction to bile flow from other structures

In this case, the brevity of the history and lack of other alarm features make the fist diagnosis less likely. Also, as mentioned earlier, choledocholithiasis is more commonly associated with biliary colic. In this case, it is necessary to get further cross sectional imaging as a matter of urgency, and to consider other causes of jaundice.

Further investigations

Following an ultrasound, CT would be the next investigation. Tumour markers such as CA19-9 have some supportive role in the diagnosis of pancreatic cancer but have a poor sensitivity and specificity [19,20]. In cases of non-malignant jaundice, Immunoglobulin subgroups, namely immunoglobulin G4 (IgG4) should also be measured.

Case Vignette (continued)

Further cross sectional imaging with a CT scan revealed extra–hepatic ductal dilatation and there was differential enhancement of the pancreas, described as "Sausage shaped" with no pancreatic duct dilatation.

The patient went on to have an ERCP (Fig 2), which revealed structuring of the distal common bile duct, which was relieved with insertion of a plastic stent; following this procedure his jaundice improved. Brush cytology was also obtained which was negative for malignant cells. His blood tests revealed raised levels of IgG4 and he was started on a course of oral corticosteroids. A diagnosis of Auto immune pancreatitis was made and his symptoms of biliary obstruction improved over the next six weeks, following which repeat ERCP confirmed improvement of the stricture enabling removal of the biliary stent (figure 2(b))

Biliary obstruction

Choledocholithiasis is the most common cause of biliary obstruction and cancer of the head of pancreas is most common cause of a malignancy causing biliary obstruction[21]. Other malignancies that can cause external compression of the biliary

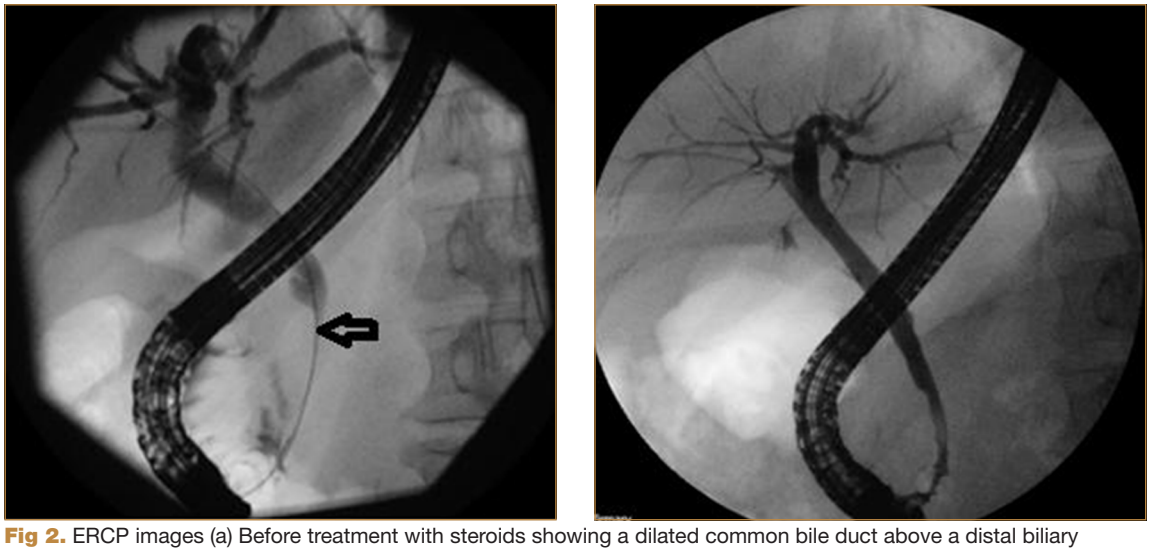

Fig 2. ERCP images (a) Before treatment with steroids showing a dilated common bile duct above a distal biliary stricture (arrow) and (b) Following treatment with steroids, showing improvement in the stricture.

tract include lymphoma, cholangiocarcinoma and infiltrating small bowel cancers.

A "sausage shaped" pancreas on cross sectional imaging with diffuse enlargement of the pancreatic tissue is highly suggestive of autoimmune pancreatitis (AIP)[22]. Narrowing of the main pancreatic duct may also be seen.

Autoimmune pancreatitis (AIP)

AIP is an IgG4 related chronic inflammatory condition which can present with obstructive biliary symptoms resulting from diffuse or focal enlargement of the pancreas tissue. It can present with an isolated pancreatic involvement but can also be associated with a wider IgG4 related autoimmune condition involving other organs[23]. It is a rare disorder with some journals quoting an incidence and prevalence of 1.4 and 4.6 per 100,000 respectively[24]. AIP has been described in up to 6% of patients who underwent resection for suspected pancreatic cancer[25]. Sclerosing changes in extra-pancreatic bile ducts (resembling PSC), diabetes mellitus and retroperitoneal fibrosis are associated with extra pancreatic involvement in IgG4 disease.

AIP can be difficult to distinguish from pancreatic malignancy[26] although the former is associated with a much better prognosis and is amenable to treatment with corticosteroids[27]. Raised levels of IgG4 are suggestive, but not diagnostic of AIP, and may be found in some cases of pancreatic cancer[28] with a possible association between these diagnoses[29]. Careful follow-up is therefore required with early involvement of a specialist pancreaticobiliary team.

Case Conclusion

The case described above was managed conservatively with immune-suppression and the patient remained symptom free under follow up. This case highlights the complexity that can sometimes be associated with diagnosing and managing a case of jaundice. Biliary obstruction should be considered even when the ALT is disproportionately elevated. A systematic approach to the evaluation of such patients and early involvement of specialists can be very beneficial.

Conflicts of Interest

None

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