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Case Report

A Successfully Managed Case of Fulminant Hepatic Failure Secondary to Ibuprofen

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Case report

We report a case of a 33-year-old female who presented at midnight with a 3-day history of lethargy, Right Upper quadrant persistent pain and vomiting more than ten times a day. She denied any symptoms of chest pain, shortness of breath, and coughing. She denied any history of fevers and rigors. She had a normal bowel habit without any diarrhoea and she did not have any haematemesis. She also did not report any urinary symptoms. She had a past medical history of migraines. She lived with her mother and was not currently working. She had no history of cigarette smoking or alcohol. She was not on any regular medications and she had no drug allergies. She denied taking any herbal or dietary supplements, paracetamol/Co-codamol and she denied ingesting any mushrooms which could have exposed her to the Amanita toxin.

On arrival to the accident and emergency department, she had an early warning score of 4; her oxygen saturations were 99% on room air, her respiratory rate was 14 breaths per minute, her temperature was 36.7 degrees Celsius, her heart rate was 117 beats per minute, and her blood pressure was 85/50. On arrival, she was pale and mildly jaundiced. She was not encephalopathic and she did not have any clinical signs of chronic liver disease.

Her Glasgow coma scale (GCS) was 15/15, her cardiovascular and respiratory examination was normal. On abdominal examination, she was tender in the right upper quadrant, but there were no signs of peritonism, and her bowel sounds were present.

Her venous blood gas on admission was the following; PH 7.26, Bicarbonate 15, Lactate 7, BM 1.8. She was aggressively hydrated with intravenous saline and intravenous dextrose to correct her hypoglycaemia. She had a full septic screen (which was all negative) and she was started on intravenous broad-spectrum antibiotics. She was also started on NAC. (N-acetylcysteine) After receiving 2.5 litres of intravenous saline, her repeat venous blood gas was as follows; PH 7.29, bicarbonate 15.8, lactate of 4.1 and blood glucose of 6.0.

Her blood tests results were as follows; Haemoglobin(Hb) 118 grams per litre, white cell count (WCC) 11.9, platelets normal, Mean Corpuscular Volume (MCV) normal, CRP<5, U&E normal, eGFR>90, pregnancy test negative, paracetamol levels<10, Salicylates levels normal, ALT 621, AST 748, Bilirubin 57, ALP normal, Albumin normal, INR 3.8, APTT 38.1, magnesium normal, Phosphate normal, Lipase normal, and ethanol levels were in range. She had a full non-invasive liver screen; Her hepatitis A, E, B, C screen was negative. Her Cytomegalovirus screen, Epstein Barr virus screen, varicella zoster virus screen, herpes simplex virus screen and leptospirosis screen were all negative. Her Wilson's disease screen was negative. Her autoimmune liver screen was negative.

She had an urgent CT abdomen and pelvis with contrast which was reported as follows; 'The appearance of the bowel and mesentery suggests acute colitis, however there was no evidence of ischaemia or perforation. There was no evidence of hepatic or portal vein thrombosis and her hepatic artery was completely patent.'

The on call general surgical team was contacted due to concerns of a surgical cause of her abdominal pain given her CT scan findings. The intensive care team was also involved early on to assess this patient to be admitted and monitored in an intensive care setting. The surgical team agreed to accept this patient under there care until an exploratory laparoscopy was done the following morning.

The following morning an exploratory laparoscopy was performed, and it was completely normal apart from an unhealthy-looking liver. After her laparoscopy, this patient was transferred to a high dependency unit level 2 bed for closer monitoring.

On a further revisit of the patient's history, including a collateral history from the mother, it came to light that she had been ingesting excessive amounts of ibuprofen of approximately more than 3000mg a day for the last 10 days prior to admission for a persistent toothache.

This patient was subsequently transferred to a quaternary centre intensive care unit with access to a liver transplant service due to a worsening coagulopathy. (her INR the following day was 4.1) She subsequently on arrival developed a Grade 3 encephalopathy and required invasive intubation of her airway. She was then put as a priority on the Liver transplant list in the UK. She however made a spontaneous hepatic recovery in 2 weeks and did not require a liver transplant. She was eventually discharged safely back to her home and has made a remarkable recovery.

Acute Liver Failure

The most commonly accepted definition of acute liver failure is a liver injury in combination with a coagulopathy and encephalopathy in a patient without any history of known liver disease, where the total duration of the illness is less than 26 weeks. Strictly speaking, In the absence of encephalopathy with all the previous features present, we define the condition as an acute severe hepatitis. However acute severe hepatitis can very quickly progress to fulminant hepatic failure depending on certain prognostic factors which will be discussed later

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in this section. A chronic liver injury is defined as an illness where the duration is greater than 26 weeks [1].

Acute liver failure can be further subcategorized into 3 categories depending on the duration between the onset of jaundice and the onset of encephalopathy. Hyperacute is defined as less than 7 days, acute as between 7 to 21 days and subacute as between 21 days to 26 weeks. A prognosis has been attached to these 3 categories with hyperacute liver failure having a more favourable prognosis than subacute liver failure. However, the American Association for Study of the Liver Diseases guidelines state this further categorisation is unnecessary as it does not have a significant effect on the prognosis. The prognosis is in fact most dependent on 3 features; the age of the patient, the aetiology of the liver failure and the degree of encephalopathy on presentation [2].

Around 17% of patients with acute liver failure have no identifiable cause and this is termed seronegative hepatitis [1,2].

Hepatitis E is a significant cause of acute liver failure in south-east Asia, India, Pakistan, and China. In the USA and Western Europe, drugs are a more common cause than viral hepatitis [1,2].

Other causes of acute liver failure worldwide include the following;

• Paracetamol overdose, • Drug-induced, • Hepatitis B, C, A, • Epstein-Barr virus, • Cytomegalovirus, • leptospirosis, • Ischaemia, • Autoimmune liver disease, • Pregnancy related (acute fatty liver of pregnancy, HELLP)

• Wilson's disease, • Budd-Chiari syndrome, • Toxins (amanita phalloides mushrooms). Table 1.

Drug induced Liver injury (DILI)

The most widely accepted definition of DILI includes elevation in ALT or AST > 5 × ULN (upper limit of normal) without symptoms or rise in alkaline phosphatase >2 × ULN or rise in bilirubin >2 × ULN in bilirubin with any rise in AST and ALT elevation. Alternatively, AST or ALT < 5 ULN with symptoms also defines DILI [3].

After paracetamol, anti-microbials are the commonest cause of drug induced liver injury in the western world. A lot of the non-paracetamol drug induced liver injuries appear to be idiosyncratic reactions with no specific relation to dose and duration of exposure. Clinically apparent drug induced liver injury due to Non-Steroidal Anti-inflammatory Drugs are 4-10 per 100,000 prescriptions and due to ibuprofen, itself is 1.0-1.6 cases per 100,000 prescriptions. It is also worth noting that only about 10% of idiosyncratic drug induced liver injuries progresses to fulminant hepatic failure, however when it occurs, about 60% end up requiring a liver transplant [4].

Several Convincing reports have been published of acute liver failure due to ibuprofen usually after presentation with an immunoallergic-like reaction within days of starting the drug [4].

The LiverTox Website is a collaboration of the National Institute of Diabetes and Digestive and Kidney Diseases, the National Library of Medicine, and the Drug Induced Liver Injury Network, including herbal and dietary supplements. A search on the LiverTox website and PubMed (the national library of medicine) have identified 5 case reports of fulminant hepatic failure attributed possibly to ibuprofen.

Table 1: Geographic variation in the aetiology of acute liver failure [1].

	United Kingdom	United States	France	India	Japan	Spain
Acetaminophen	54%	46%	2%	-	-	2%
Drug reactions	7%	12%	15%	5%	-	17%
Seronegative	17%	14%	18%	24%	45%	32%
Hepatitis A or B	14%	10%	49%	33%	55%	37%
Hepatitis E	-	-	-	38%	-	-
Other causes	8%	18%	16%	-	-	12%

These were in the years; 1986,2002,2007,2011 and 2014. Most recently a case report was published in 2018 in The Cureus Journal of Medical Science.

Given the that the patient in our case had a completely negative non-invasive liver screen and all other drug causes had been ruled out, it is likely this was liver failure induced by ibuprofen. Although the patient did not have a liver biopsy to confirm the diagnosis, the nature of the patient's presentation within days of taking the drug and having never taken ibuprofen or any other drug before, it is again another indication that favours this aetiology.

General principles of management in Acute liver failure

Early recognition and prompt assessment of acute liver failure cases with recognition of the underlying aetiology is the key to successfully managing acute liver failure patients. It is important to manage such patients early on an in intensive or high dependency setting to be able to closely monitor them in case sudden deterioration occurs [5].

Early assessment and evaluation of referral to a liver transplant service is vital to successful management. The most widely accepted criteria used is the King's college criteria for paracetamol and non-paracetamol causes [5].

For non-paracetamol causes;

Prothrombin time >100 seconds (irrespective of grade of encephalopathy) or Any three of the following (irrespective of grade of encephalopathy) indicate early referral for a liver transplant:

(1) aetiology; seronegative hepatitis, halothane hepatitis, idiosyncratic drug reactions

(2) age<10 or > 40 years

(3) jaundice to encephalopathy interval >7 days

(4) prothrombin time >50 seconds

(5) serum bilirubin >300 μmol/l.

On the King's college criteria above, our patient however was scoring a 2 for aetiology and her Prothrombin time. However, the British Society of Gastroenterology (BSG) makes specific recommendations for non-paracetamol causes of acute liver failure. The following is advised; 'Patients with non-paracetamol acute and subacute liver failure (defined by the presence of encephalopathy) (including fulminant Wilson's disease) should be referred to a transplant centre + Patients with non-paracetamol liver failure and a progressive coagulopathy in the absence of encephalopathy should be discussed with a transplant centre.' In our case, our patient's coagulopathy was rapidly worsening on day 2 and even though she had no clinical evidence of encephalopathy, the BSG guidance was used and used correctly given that she deteriorated later and thus ended up requiring invasive intubation of her airway [5].

The full clinical picture should also always be taken into context when evaluating acute liver failure patients. In our case, the findings on the CT scan was a likely red herring and an invasive investigation like an exploratory laparoscopy could have possibly been avoided.

Cerebral oedema is an important cause of death due to uncal herniation and hypoxic brain injury. It can be predicted by the degree of encephalopathy. Kidney injury commonly occurs and therefore close monitoring of haemodynamic status and avoidance of all nephrotoxic drugs is essential. Prophylactic antibiotics is recommended to prevent worsening encephalopathy and subsequent cerebral oedema. Routine correction of coagulopathy is not recommended unless bleeding

occurs, due to masking the progression of acute liver failure. Early nutritional support and regular monitoring of the blood glucose levels is highly recommended due to the liver's inadequate degradation of insulin and its inadequate production of glucose [6-8].

Conclusion

Our case highlights several important learning points. Firstly, we are attempting to publish the 7th official case report of fulminant hepatic failure due to ibuprofen. Although most cases of ibuprofen induced liver injury appear to be idiosyncratic, a recent case control study in the British Journal of Clinical Pharmacology in 2016 has shown that the incidence of acute liver injury appears to be higher when ingesting more than 1200mg a day. This study supports the findings in our case and the most recent case report in 2018 in The Cureus Journal of Medical Science which was due to an ibuprofen overdose. Our case is also a case of acute liver failure without an immunoallergic like reaction, something that is atypical for ibuprofen related liver failure. Secondly, even though the King's college criteria is a widely accepted system used to evaluate patients for referral to a liver transplant unit, we still want to highlight the importance of the Recommendations given in the indications of referral for liver transplantation in the British Society Of Gastroenterology (BSG) guidelines when evaluating patients for a liver transplant. We recommend that all patients with non-paracetamol liver failure and a progressive coagulopathy in the absence of encephalopathy should be discussed with a transplant centre. Finally, we report a rare successfully managed case of fulminant hepatic failure likely due to ibuprofen with spontaneous hepatic recovery after withdrawal of the offending agent.

References

1. Lee WM, Squires RH Jr, Nyberg SL, Doo E, Hoofnagle JH (2008) Acute liver failure: Summary of a workshop. *Hepatology* 47: 1401-1415. [crossref]
2. Lee WM, Stravitz RT, Larson AM (2012) Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. *Hepatology* 55: 965.
3. Mochida S, Takikawa Y, Nakayama N, et al. (2011) Diagnostic criteria of acute liver failure: A report by the Intractable Hepato-Biliary Diseases Study Group of Japan. *Hepatol Res* 41: 805.
4. Lee WM (2008) Etiologies of acute liver failure. *Semin Liver Dis* 28: 142-152. [crossref]
5. Muñoz SJ (1993) Difficult management problems in fulminant hepatic failure. *Semin Liver Dis* 13: 395.
6. Agarwal B, Wright G, Gatt A, et al. (2012) Evaluation of coagulation abnormalities in acute liver failure. *J Hepatol* 57: 780.
7. Tujios SR, Hynan LS, Vazquez MA, et al. (2015) Risk factors and outcomes of acute kidney injury in patients with acute liver failure. *Clin Gastroenterol Hepatol* 13: 352.
8. Chavarria L, Alonso J, Rovira A, Córdoba J (2011) Neuroimaging in acute liver failure. *Neurochem Int* 59: 1175.