Case report

Wilson disease: a diagnostic challenge in a patient with alcoholic liver disease

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Accepted 10 October 2019

SUMMARY

A 32-year-old man with alcoholic cirrhosis presented with worsening abdominal distension and jaundice. He was diagnosed with cirrhosis 2 years prior after a hospitalisation for acute liver failure, during which viral, autoimmune and metabolic workup was unrevealing. Heavy alcohol consumption was his only obvious risk factor for liver disease, so his decompensation was attributed to alcohol. At the present time, he was admitted with acute-on-chronic liver failure and acute renal failure. The severity of his presentation and the disproportionately mild elevation in alkaline phosphatase relative to his hyperbilirubinaemia prompted repeating a ceruloplasmin level, which, though previously normal, was now low, and eventually led to a diagnosis of Wilson disease (WD) with concomitant alcoholic liver disease. Clinicians must recognise limitations in ceruloplasmin and copper levels when screening for WD and maintain suspicion for WD in young patients, even if there is an already established aetiology of liver disease.

BACKGROUND

Wilson disease (WD) is a rare, autosomal recessive disorder of copper metabolism, resulting in copper accumulation in the liver and other organs, including the central nervous system and kidneys.[1] Involvement of other organs typically follows liver involvement, reflecting copper accumulation after liver saturation.[2] The estimated prevalence of WD is 1 case per 30 000 live births.[3] WD arises from a chromosome 13 defect, resulting in loss-of-function of the ATP7B protein involved in copper transport across the trans-Golgi membrane into transport vesicles.[4] WD is associated with over 500 disease-causing mutations, resulting in a wide phenotypic spectrum, ranging from asymptomatic biochemical derangements to fulminant liver failure.[5 6] Thus, diagnosing WD requires a high index of suspicion. Liver transplantation is the only definitive treatment for acute liver failure due to WD, so prompt and accurate diagnosis is critical.[1] The coexistence of WD and alcoholic liver disease (ALD) has not been well described in literature. Patients with WD and ALD may exhibit features of both aetiologies, and screening tests such as ceruloplasmin may be misleading.

CASE PRESENTATION

A 32-year-old man with history of alcoholic cirrhosis presented with 2 weeks of worsening abdominal distension and skin yellowing.

He was diagnosed with cirrhosis 2 years prior after presenting in acute liver failure. During his previous hospitalisation, he reported 10 years of significant alcohol consumption, typically drinking either 32 ounces of beer or 10 shots of liquor daily. Imaging revealed a cirrhotic-appearing liver and ascites. Other than alcohol, he had no other obvious risk factors for liver disease. He did not smoke, use illicit drugs, or take supplements or medications, including over-the-counter drugs. Laboratory studies at this initial encounter are shown in table 1, notable for a normal creatinine and macrocytosis without overt anaemia.

Liver profile was consistent with a cholestatic pattern with a slightly elevated international normalised ratio. Autoimmune markers, including antinuclear antibodies, antimitochondrial antibodies and antismooth muscle antibodies, were negative, as were serology markers for viral hepatitis. Ceruloplasmin and serum copper were within normal range. His Maddrey discriminant function was 16.5, so he did not receive steroids. He was treated conservatively with supportive care, and his transaminases normalised. Total bilirubin improved from 10.1 to 6.8 mg/dL at the time of discharge. Subsequently, he was lost to follow-up until his present admission.

At his present admission, the patient's social history was unchanged, with continued consumption of five shots of liquor daily. His last drink was 2 weeks prior to admission. Family history was notable for oesophageal cancer in his father; otherwise, there was no family history of liver disease, though he had no siblings. He denied fevers, vomiting, bleeding, or changes in bowel movements. He did note a decrease in urine volume. Physical examination on admission was notable for jaundice with markedly icteric sclera and a diffusely tender, protuberant abdomen with a fluid wave. He was awake and fully oriented, without asterixis, on initial evaluation. During the hospitalisation, he became increasingly confused and lethargic. Subsequent physical examinations were notable for the development of asterixis and worsened abdominal distension with bilateral pitting oedema.

INVESTIGATIONS

Laboratory studies are listed in table 1. Liver profile included alanine transaminase (ALT) 51 U/L (reference 10–50 U/L), aspartate aminotransferase (AST) 113 U/L (reference 10–50 U/L) and alkaline phosphatase (ALP) 153 U/L (reference 40–129 U/L).

To cite: Patel R. *BMJ Case Rep* 2019;**12**:e232449. doi:10.1136/bcr-2019-232449

Table 1 Laboratory studies during the patient's current admission compared with the initial encounter 2 years prior

Laboratory study	Admission 1 (2 years prior)	Admission 2	Reference range
Sodium (mmol/L)	139	128	135–145
Potassium (mmol/L)	4.0	2.9	3.6–5.0
Chloride (mmol/L)	101	89	98–109
Bicarbonate (mmol/L)	26	20	22–31
Blood urea nitrogen (mg/dL)	4	79	6–23
Creatinine (mg/dL)	0.55	7.31	0.67–1.17
Albumin (g/dL)	3.0	2.4	3.5–5.2
Aspartate aminotransferase (U/L)	199	113	10–50
Alanine aminotransferase (U/L)	96	51	10–50
Alkaline phosphatase (U/L)	132	153	40–129
Bilirubin, total (mg/dL)	10.1	38.5	0.2–1.3
Bilirubin, conjugated (mg/dL)	4.9	>20	0.0–0.3
International normalised ratio	1.4	3.6	0.9–1.1
White blood cell count	7×10^9/L	21.24×10^9/L	$4.22–10.33\times10^9$/L
Haemoglobin (g/L)	137	98	132–169
Mean corpuscular volume (fL)	103.2	92.9	79.0–92.2
Platelet count	242×10^9/L	245×10^9/L	$160–383\times10^9$/L
Ferritin (ng/mL)	869	750	30–400
Gamma glutamyl transferase (U/L)	Not performed	105	8–61
IgA (mg/dL)	Not performed	464	70–400
Ceruloplasmin (mg/dL)	26	17.6	19–31
Copper, serum (µg/dL)	132	62	63.7–140.12
Copper, urine 24 hours (µg/24 hours)	Not performed	67	3–50
Hepatitis A virus antibody IgG	Reactive	Reactive	Non-reactive
Hepatitis B surface antigen	Non-reactive	Non-reactive	Non-reactive
Hepatitis B core antibody	Non-reactive	Non-reactive	Non-reactive
Hepatitis B surface antibody	Reactive	Reactive	Non-reactive
Hepatitis C antibody	Non-reactive	Non-reactive	Non-reactive
Peritoneal fluid, nucleated cells/µL	74	69	≤499/µL
Peritoneal fluid, albumin (g/dL)	0.4	0.3	N/a
Peritoneal fluid, protein (g/dL)	0.8	0.4	N/a
Peritoneal lactate dehydrogenase (U/L)	49	Not performed	N/a

N/a, not applicable.

Total bilirubin was 38.5 mg/dL (reference 0.2–1.3 mg/dL), with direct bilirubin >20 mg/dL (reference 0.0–0.3 mg/dL). Viral serology indicated immunity to hepatitis A and B and a non-reactive hepatitis C antibody test. Basic metabolic panel was notable for creatinine of 6.7 mg/dL (baseline 0.5 mg/dL during prior admission). Haemoglobin was 98 g/L on admission and dropped to 65 g/L during the course of his hospitalisation (reference 132–169 g/L). Mean corpuscular volume was minimally elevated to 92.9 fL (reference 79.0–92.2 fL). White blood cell count was 21.24×10^9/L (reference $4.22–10.33\times10^9$/L). Paracentesis was performed; peritoneal fluid contained 69 nucleated cells/µL, and fluid protein was 0.4 g/dL. His serum to ascites albumin gradient was 2.1 g/dL. Peritoneal fluid gram stain and cultures were negative. Thus, peritoneal fluid was consistent with cirrhosis and was not indicative of spontaneous bacterial peritonitis. Blood and urine cultures did not grow organisms. Abdominal ultrasound and abdominal CT scan on admission were consistent with cirrhosis and noted large volume ascites, similar to previous imaging.

DIFFERENTIAL DIAGNOSIS

It was presumed that our patient was presenting with decompensated ALD, given his prior diagnosis of alcoholic cirrhosis, continued alcohol consumption, and previously unremarkable workup. His hospital course was marked by worsening encephalopathy, significant renal disease in the absence of a recognisable toxic exposure that required dialysis, and a suspected haemolytic anaemia, given his worsening anaemia without an obvious source of bleeding. His clinical deterioration prompted reassessing the differential for acute liver failure.[1] Acute viral hepatitis was again excluded based on negative serologic markers. Drug-induced liver injury was unlikely given the lack of an offending agent, and laboratory studies were inconsistent with this pattern of liver injury.[7] Autoimmune hepatitis was less likely given the negative autoimmune workup and normal IgG; furthermore, autoimmune hepatitis is associated with a higher elevation in the transaminases (5–10 times the upper limit of normal) with a relatively milder effect on ALP.[7 8] The severity of disease at his young age and the disproportionately mild ALP elevation relative to his hyperbilirubinemia raised concern for WD despite the normal ceruloplasmin during previous workup.[9] Ceruloplasmin was repeated and was low at 17.6 mg/dL (reference >20 mg/dL). Kayser-Fleischer rings, which result from copper deposition in Descemet's membrane of the cornea,[10] were identified on slit-lamp examination by two separate ophthalmologists. Twenty-four-hour urine copper was elevated at 62 µg/24 hours (reference 3–50 µg/24 hours).

According to the American Association for Study of Liver Diseases, WD can be diagnosed without liver biopsy or molecular testing by the following criteria: serum ceruloplasmin <20 mg/dL, Kayser-Fleischer rings present, and 24-hour urine copper >40 µg.[1] Our patient was diagnosed with WD by these criteria without the need for biopsy or molecular testing.

TREATMENT

The Maddrey discriminant function for alcoholic hepatitis was 91; thus, prednisone was started after infection was excluded.[11] The patient continued to deteriorate while on prednisone. After he was diagnosed with WD, he continued receiving prednisone because it was suspected that his underlying ALD was also contributing to his presentation. Additionally, he was started on zinc. Zinc interferes with the uptake of copper from the gastrointestinal tract by inducing a protein that binds to copper with high affinity and results in its loss in faecal contents.[12] Though acute liver failure due to WD requires urgent liver transplantation, our patient's lack of insurance and on-going alcohol use posed barriers to immediate transplant. Plasmapheresis and exchange transfusion (PLEX) was initiated with the intent of reducing serum copper to delay his need for transplantation and prevent further copper-mediated renal tubular damage. The patient's mental status returned to baseline, and his renal function recovered. He was stabilised through these measures with a plan to continue supportive therapy and prevent further damage while he works to become a transplant candidate.

OUTCOME AND FOLLOW-UP

The patient's mental status returned to baseline, and his renal function recovered while on PLEX. He was stabilised through these measures with a plan to continue supportive therapy and prevent further damage while he works to become a transplant candidate. The duration and frequency of PLEX to continue supportive therapy are unclear at this time.

DISCUSSION

WD poses a diagnostic challenge, given the broad spectrum of clinical phenotypes. Diagnosis is especially difficult in patients with multiple aetiologies of liver failure. This challenge has been described in other cases. One such case of a patient with hepatitis E associated liver failure and subsequent diagnosis of fulminant WD requiring urgent transplantation proposed that decompensation in WD may be precipitated by an acute hepatic insult, such as infection.[13] Other cases have described patients with acute liver failure found to have WD with concomitant acute varicella infection,[14] autoimmune hepatitis[15] and non-alcoholic steatohepatitis.[16] Altogether, a proactive diagnostic evaluation for WD in the correct clinical context should be pursued when patients are not responding as expected to appropriate therapy.

Our patient had a known history of heavy alcohol use and a thorough prior viral, autoimmune, and metabolic workup for acute liver failure that was unremarkable. The pattern biochemical tests, including AST to ALT ratio >2.0 and elevated ferritin, gamma-glutamyl transferase (GGT), IgA and mean corpuscular value, were consistent with underlying ALD.[8] While ALD likely contributed to his clinical picture, the severity of liver disease at his young age prompted further evaluation.

Though ceruloplasmin is often used to screen for WD, it is an acute phase reactant and may be increased in any inflammatory state, including acute liver failure.[16] Ceruloplasmin may be elevated to the lower limit of normal in 20% of WD patients.[16] Alternatively, cirrhosis, regardless of aetiology, may result in a low ceruloplasmin level.[17] Ceruloplasmin <20 mg/dL has a diagnostic sensitivity of 21%–56% and specificity of 63%–84% for WD, depending on laboratory methodology.[18] Elevated free serum and 24-hour urine copper levels are also not specific for WD. Copper excretion into the bile can be impaired in acute liver failure regardless of aetiology, and any cholestatic process can cause hepatic copper accumulation.[18] Total serum copper includes copper incorporated in ceruloplasmin; thus, though WD is a disease of copper excess, measured serum copper can be low due to decreased ceruloplasmin. Alternatively, liver failure in WD may lead to sudden release of copper from tissue stores, elevating serum copper.[18] Though possible to estimate non-ceruloplasmin bound copper, a reliable level depends on accuracy in measuring serum copper and ceruloplasmin, both of which can be altered by different disease states.[5 19]

Hyperbilirubinemia out of proportion to modest transaminase elevation may aid in differentiating fulminant liver failure due to WD from other causes.[9] A comparison of acute liver failure secondary to WD versus other conditions demonstrated that a ratio of ALP to total bilirubin <4.0 is 94% sensitive and 96% specific to diagnose WD. Additionally, the study found an AST to ALT ratio >2.2 is 94% sensitive and 86% specific to diagnose WD.[18] Sensitivity and specificity for WD in the context of acute liver failure approached 100% when the two ratios were combined.[18] Our patient's biochemical profile was suggestive of WD, given ALP to total bilirubin ratio of 3.97 and AST to ALT ratio of 2.22.[18]

Our patient presented with acute renal failure and a suspected haemolytic anaemia, fairly non-specific features in liver disease; however, it is important to consider WD when present in young patients with liver failure. While the mechanism of renal failure in WD is unclear, it has been associated with tubular dysfunction from copper toxicity.[20 21] Tubular disease in WD may respond to chelation therapy, possibly due to a relationship with copper excess.[20] In addition to his chronic macrocytic anaemia, our patient's fluctuating severe anaemia without an obvious source of blood loss raised suspicion for haemolysis. Though our patient's anaemia was not worked up further as his haemoglobin stabilised after PLEX initiation, a Coombs-negative haemolytic anaemia is recognised as a significant feature in WD.[1] A large Japanese study found that haemolytic anaemia was the sole presenting feature of WD in 3 of 282 patients and was present in 28% of patients who presented with jaundice.[22] The anaemia is presumably due to intravascular haemolysis triggered by copper release from dying hepatocytes and resulting disruption of red blood cell membranes, perhaps contributing to the disproportionate elevation of AST compared with ALT associated with WD.[18 21]

Clinicians should maintain a high suspicion for WD in patients presenting with severe liver failure at age <40 years, even when there is a previously established aetiology of disease.[8] Features of multiple aetiologies of liver disease may be present, and limitations of screening tests such as ceruloplasmin can make diagnosis difficult.

Learning points

- Wilson disease (WD) poses a diagnostic challenge because serum ceruloplasmin may be elevated to a value within normal range since it is an acute phase reactant, and patients with liver failure regardless of aetiology may present with an elevated 24-hour urine copper and a low ceruloplasmin.
- Acute renal failure and haemolytic anaemia and may accompany acute liver failure due to WD.
- An alkaline phosphatase to total bilirubin ratio <4 with an AST to ALT ratio >2.2 can aid in screening for WD.
- This case highlights the importance of maintaining a thorough differential in patients with an already established and more obvious aetiology of liver disease and demonstrates that patients may present with manifestations of multiple aetiologies of liver injury.

Contributors RP contributed towards acquiring patient consent, coordinating patient information, writing and editing the case report.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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