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Case Report

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Wilson's disease or autoimmune hepatitis? A case report of two great mimics clashing

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Abstract

Wilson disease and autoimmune hepatitis are two major causes of liver injury with overlapping clinical and laboratory features, making etiological diagnosis particularly challenging. As management differs substantially between the two conditions, inability to distinguish between them may lead to disease progression, liver failure or even the need for liver transplantation if proper therapy is delayed.

We present the case of a 22-year-old male patient with a mild neuropsychiatric history who was admitted with acute liver injury. Clinical and laboratory evaluation initially pointed towards Wilson disease, with a Leipzig score of 4 derived from the presence of Kayser–Fleischer rings and increased 24-hour urinary copper excretion. Chelation therapy with D-penicillamine resulted in only transient clinical and biochemical improvement. Therefore, corticosteroid therapy was subsequently introduced, despite negative autoimmune serology because autoimmune hepatitis could not be excluded. This resulted in a striking clinical and biochemical response. Genetic testing of the ATP7B gene was negative for pathogenic variants, while liver biopsy could not be performed because of clinical and patient-related limitations.

This case highlights the diagnostic challenges posed by overlapping features of Wilson disease and autoimmune hepatitis and illustrates the limitations of currently available diagnostic tools in establishing a definitive diagnosis.

Keywords: Wilson's disease; Autoimmune hepatitis; Acute liver injury; Acute liver failure.

Abbreviations: WD: Wilson Disease; AIH: Autoimmune Hepatitis.

Introduction

Acute liver failure is an uncommon but life-threatening clinical syndrome characterized by the rapid development of severe hepatic dysfunction, coagulopathy, and encephalopathy in a patient without known pre-existing liver disease. In young adults presenting with jaundice and acute hepatic decompensation, early recognition of the underlying cause is essential, because prognosis and management depend heavily on timely etiologic diagnosis, including the need for urgent referral to a liver transplant center [1].

The differential diagnosis of acute liver failure is broad and includes drug-induced liver injury, acute viral hepatitis, toxin exposure, ischemic or vascular liver injury, metabolic disorders, and autoimmune hepatitis. Although common causes must be

promptly excluded, rare etiologies are particularly important in younger patients because they may be rapidly progressive, diagnostically challenging, and potentially treatable if recognized early [2].

Among these, Wilson disease remains a critical consideration. As an inherited disorder of copper metabolism, Wilson disease may present with acute severe hepatitis or fulminant liver failure, sometimes without a previously established diagnosis [3]. Autoimmune hepatitis is another important cause of acute severe hepatitis and acute liver failure [4]. Distinguishing Wilson disease from autoimmune hepatitis can be challenging because both may share biochemical, serological, and histological features. Wilson disease can mimic autoimmune hepatitis through autoantibody positivity, hypergammaglobulinemia, and interface hepatitis, while seronegative autoimmune hepatitis may lack typical serological markers [5]. This distinction is clinically important because management differs substantially, ranging from immunosuppression to urgent transplant assessment.

We report the case of a 22-year-old man who presented with jaundice and acute liver failure on a background of otherwise limited medical history, remarkable only for mild intellectual disability. The case illustrates the diagnostic challenge of acute liver failure in a young adult, particularly when Wilson disease and seronegative autoimmune hepatitis remain plausible competing diagnoses.

Case description

A 22-year-old male residing in a social services facility presented to the emergency department of a tertiary hospital, following progressive weakness and jaundice, with an acute onset. The patient's medical history was significant from a neuropsychiatric standpoint, since he had been diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD), conduct disorder, and mild intellectual disability. Apart from these, a history of thrombocytopenia requiring hospitalization was also reported. Prior to admission, his outpatient medication regimen included olanzapine, biperiden, valproate, zuclopenthixol, chlorpromazine, diazepam and levothyroxine.

The patient was admitted due to acute liver injury and severe hyperbilirubinemia. Due to the severity of the hepatic insult, he was transferred to our center for specialized hepatological management. Upon initial clinical evaluation, the patient was febrile (37.8°C), tachycardic (100 beats per minute), and normotensive (135/90 mmHg). Abdominal examination revealed hepatosplenomegaly, without localized tenderness. Neurologically, he exhibited a fluctuating level of consciousness, with an initial Glasgow Coma Scale (GCS) score of 10/15.

Laboratory evaluation (Table 1) confirmed acute liver injury characterized by a prominent hepatocellular pattern. Marked transaminasemia was observed, with Alanine aminotransferase (ALT) and aspartate Aminotransferase (AST) levels reaching more than 15 times the Upper Limit of Normal (ULN). Marked direct hyperbilirubinemia and elevated Alkaline Phosphatase (ALP) and Gamma-glutamyl Transferase (γ-GT) levels were noted. The International Normalized Ratio (INR) became progressively prolonged.

An extensive workup was performed to identify the driver of the acute injury:

- **Infectious causes:** Initial and repeat serological and molecular testing for Hepatitis A Virus (HAV), B (HBV), C (HCV), and E (HEV), Cytomegalovirus (CMV), Epstein-Barr Virus (EBV), Herpes Simplex Virus (HSV), Varicella-Zoster Virus (VZV), Leptospira, and Hantavirus returned negative results.

- **Autoimmune causes:** Screening for autoimmune liver diseases, including Antinuclear Antibodies (ANA-Hep2), Anti-Mitochondrial Antibodies (AMA), Anti-Smooth Muscle Antibodies (ASMA), Anti-Liver Kidney Microsomal type 1 Antibodies (anti-LKM1), and Antineutrophil Cytoplasmic Antibodies (ANCA), was negative.

- **Toxicological causes:** Serum valproic acid levels were checked and noted to be marginally below the therapeutic threshold.

- **Genetic causes:** Initial laboratory investigations revealed borderline-low serum ceruloplasmin levels. A subsequent 24-hour urinary copper collection demonstrated a threefold increase above the upper reference limit, while serum total copper levels were decreased. Furthermore, an ophthalmological consultation identified bilateral Kayser-Fleischer rings, which were confirmed upon serial reassessment. Brain Magnetic Resonance Imaging (MRI) did not demonstrate findings typical of neuropsychiatric Wilson's disease. Alpha-1 antitrypsin levels were normal.

- **Other causes:** Contrast-enhanced Computed Tomography (CT) of the chest, abdomen, and pelvis confirmed hepatosplenomegaly (Figure 1), without focal hepatic lesions or hepatic vascular thrombosis. Abdominal ultrasound and Magnetic Resonance Cholangiopancreatography (MRCP) excluded biliary tract obstruction.

Given the initial clinical constellation of acute hepatocellular injury, prolonged INR, encephalopathy, non-A, non-B hepatitis etiology, prolonged jaundice, and a total serum bilirubin concentration exceeding 17.5 mg/dL, the patient fulfilled the King's College criteria for non-acetaminophen-induced acute liver failure. Consequently, the local liver transplantation team and the National Transplant Organization were notified. Following multidisciplinary review, the patient was formally listed for emergency liver transplantation.

Based on the Leipzig scoring system, the presence of Kayser-Fleischer rings combined with the marked 24-hour urinary copper excretion yielded a total diagnostic score of 4 points, establishing a highly likely diagnosis of Wilson's disease. Confirmatively, a d-penicillamine challenge test demonstrated marked urinary copper excretion. Consequently, the aforementioned copper chelating agent was initiated. While the patient demonstrated clinical improvement, subsequent laboratory panels demonstrated an unremitting rise in transaminases and worsening hyperbilirubinemia. Although a liver biopsy would have possibly yielded important information in the context of differential diagnosis, it was not performed in our case. The reasons were the deteriorating synthetic function and the patient's neuropsychiatric background, that precluded safe cooperation. Since autoimmune hepatitis could not be excluded, following a repeat autoimmune serology sampling,

Table 1: Initial laboratory evaluation.

White Blood Cells (K/μL)	4,9	Urea (mg/dL)	27
Neurophils(K/μL)	2,6	Uric acid (mg/dL)	3.2
Hematocrit (%)	44,5	AST (SGOT) (U/L)	1343
Hemoglobin (g/dL)	14,6	ALT (SGPT) (U/L)	1193
Platelets (10^3/μL)	132	LDH (U/L)	485
PT	14,4	Fasting glucose (mg/dL)	88
aPTT	44	Total proteins (g/dL)	5.2
INR	1,31	Albumin (g/dL)	3.5
Fibrinogen (mg/dL)	326	Alkaline phosphatase(U/L)	272
D-dimmers (μg/dL)	248	γ-GT (U/L)	354
Lactate (mg/dL)	13	BilirubinTotal / Direct (mg/dL)	18,2 / 12,9
Creatinine(mg/dL)	0,91	C-reactive protein (mg/dL)	24,1 (normal values <6)

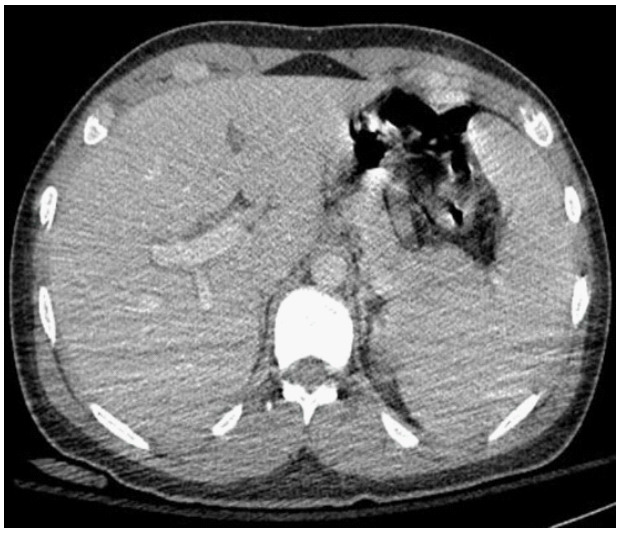

Figure 1: Contrast-enhanced computed tomography of the abdomen demonstrating hepatosplenomegaly.

corticosteroid therapy with prednisolone (at a dose of 1 mg/kg – total 80 mg/day) was introduced. From that timepoint, transaminase levels decreased rapidly, total bilirubin levels steadily declined, and the synthetic liver function normalized (Figure 2). The patient was successfully stabilized and removed from the active transplant list. He was discharged with instructions to maintain d-penicillamine and prednisolone. One month later his transaminase and bilirubin levels were almost normal. Genetic testing for Wilson's disease was negative for pathogenic and likely pathogenic variants of the ATP7B gene. Consequently, D-penicillamine was discontinued, while prednisolone therapy was maintained, as the patient's favorable response raised the possibility of an immune-mediated component to the liver injury.

Discussion

The present case reflects the complexity of the diagnostic evaluation of acute liver injury when clinical, laboratory, and imaging findings do not converge on a single diagnosis. The presence of Kayser–Fleischer rings (2 points) and increased copper excretion in a 24-hour urine collection (2 points) yielded a Leipzig score of 4, raising a high suspicion for Wilson Disease

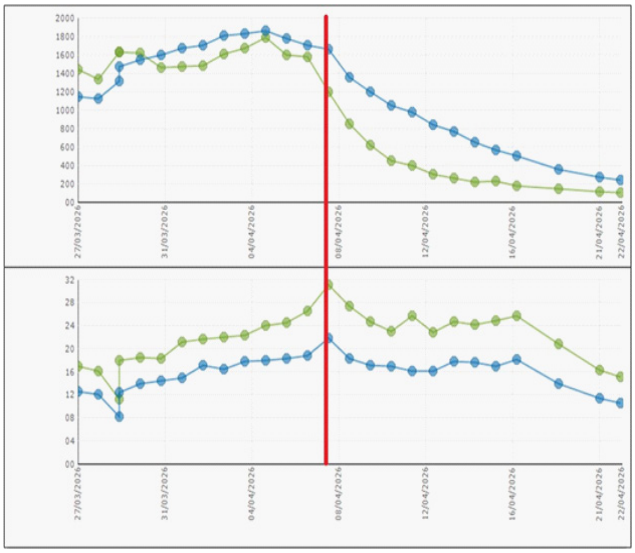

Figure 2: Transaminase and bilirubin course, before and after the initiation of prednisolone.
Upper diagram: Green line represents the course of AST, blue line represents the course of ALT.
Lower diagram: Green line represents the course of total bilirubin, blue line represents the course of direct.
Bilirubin red line: Timepoint of prednisolone initiation.

(WD). However, according to the EASL guidelines, a definitive diagnosis of WD should be established by combining the Leipzig score, genetic analysis, and the Relative Exchangeable Copper (REC) index, derived from the ratio of exchangeable copper to total serum copper [6]. The REC index was not available in our setting and therefore could not be assessed.

Given the absence of detectable autoantibodies, WD initially appeared to be the most likely diagnosis. Consequently, treatment with D-penicillamine was initiated. Nevertheless, the introduction of chelation therapy did not result in an improvement in liver function. Moreover, due to gradual biochemicl deterioration, corticosteroid therapy was initiated, considering the possibility of seronegative Autoimmune Hepatitis (AIH). The subsequent improvement in the patient's biochemical liver markers was significant.

This remarkably favorable response to corticosteroid treatment raised doubts as to whether the findings suggestive of WD were sufficient to fully explain the patient's clinical presentation.

Kayser–Fleischer rings and elevated urinary copper excretion, although strong indicators of WD, are not entirely specific findings, and their presence has been reported in other forms of acute liver injury [7,8]. Therefore, the Leipzig score may have overestimated the likelihood of WD in the present case.

The probability of WD was further questioned after genetic analysis of the ATP7B gene yielded negative results. However, in our case, genetic testing was limited to the analysis of the coding regions (exons) of the ATP7B gene. Given that more than 900 ATP7B variants have been described and that most patients with WD are compound heterozygotes [7], this negative result should be interpreted with caution. Intronic mutations or pathogenic variants located in regulatory regions of the gene may escape detection. Furthermore, large patient cohorts have shown that a proportion of clinically confirmed WD cases remain without complete genetic confirmation even after extensive molecular testing [9].

The patient's favorable response to corticosteroid therapy highlights the possible involvement of immunological mechanisms in the pathogenesis of the liver injury. Although testing for antibodies (ANA, ASMA, AMA and anti-LKM1) was negative, the possibility of AIH or an overlap between WD and AIH remained a consideration.

Importantly, even the presence of positive autoantibodies, the exclusion of WD as the principal diagnosis would still have been challenging. Literature describes a significant overlap in laboratory findings between WD and AIH [10]. In the study by Patel et al., approximately one in three patients with genetically confirmed WD had positive autoantibodies (ANA, ASMA, or anti-LKM1), whereas one in five fulfilled the diagnostic criteria for probable AIH [10]. These findings do not necessarily indicate the coexistence of the two conditions but may instead reflect immune activation secondary to hepatocellular injury in WD [10].

Of note, the diagnosis of seronegative AIH remains a significant diagnostic challenge. According to Colapietro et al., many cases initially characterized as seronegative AIH were ultimately attributed to incomplete autoantibody assessment or the absence of repeat serological measurements [11]. Particularly noteworthy is the Greek cohort included in their study, in which no patient remained truly seronegative following comprehensive reassessment [11]. These findings suggest that the absence of detectable autoantibodies alone is insufficient to exclude the diagnosis of AIH [11,12].

According to the EASL guidelines, liver biopsy remains an essential component in the diagnostic workup of AIH, as histopathological evaluation may provide valuable information in differentiating WD from AIH [12]. In our case, liver biopsy could not be performed because of the patient's neuropsychiatric condition, inability to cooperate adequately, and the perceived procedural risk. The absence of histological confirmation represents a major limitation of the present report.

Conclusion

Despite the extensive diagnostic investigation and a favorable response to corticosteroid therapy, definitive etiological classification of the patient's liver injury could not be achieved. The present case illustrates the diagnostic challenges that arise when features of two major hepatic mimics, WD and AIH, coexist or overlap, emphasizing the need for a comprehensive and individualized diagnostic approach.

Conflict of interest: The authors have no conflict of interest to report

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