

Co-Occurrence of Wilson Disease and auto-Immune Hepatitis in 14-Year-old Female: A Case Report*

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Abstract

Unusual cases of coexistence between Wilson's disease and autoimmune hepatitis have occurred. There are characteristics of both diseases in this community of patients, and laboratory and histo pathological findings can be misleading. Wilson disease's clinical appearance can differ widely; thus, there is not always an easy diagnosis. In addition to being childhood and young adult illnesses, Wilson's disease can also be triggered at any age. Liver disease and cirrhosis, neuropsychiatric disorders, Kayser-Fleischer (KF.) rings, and acute hemolysis events are the primary characteristics of Wilson's disease, frequently in combination with acute liver failure. Diagnosis is extremely difficult for children and adults with active liver disease. None of the latest Wilson's disease laboratory tests are optimal and may not be specific. Therefore, by taking into account acute hepatitis similar to Wilson's disease and autoimmune hepatitis, concomitant treatment with immunosuppression and penicillamine may have a superior impact.

Keywords: autoimmune liver disease; histopathology; wilson's disease; kayser–fleischer rings

Introduction

In Autoimmune Hepatitis, clinical, serological, histological and radiological characteristics overlap, but adequate diagnosis remains hampered by a lack of standardized diagnostic criteria. With regard to the risks and benefits of treatment, patients should be carefully consulted, taking into account the lack of randomized and monitored outcome evidence for medical interventions[1]. The coexistence of Wilson disease (WD) and autoimmune liver disease (ALD) in the same patients is a rare entity[2,3]. Necrosis of the hepatocytes and exposure of the intracellular antigen to the immune system was observed in WD, leading to the development of low-titer autoantibody[4]. WD screening is therefore highly recommended in patients classified as AIH, especially when the response to immunosuppressive drug treatment is disappointing. In this case, mixed steroid and d-penicillamine treatment may be successful. The main causes of acute and chronic hepatitis are Wilson's disease (WD) and autoimmune hepatitis (AIH). At the same time, the coexistence of these illnesses in one patient is rare. Hepatocyte necrosis and intracellular antigen exposure to the immune system is seen in

WD. This observation is a misleading excuse to differentiate AIH from WD [5]. There is no proof of dermatological indicators of autoimmune disorders and levels of serum immunoglobulin are not elevated in this group of WD patients. WD screening is highly recommended in patients classified as AIH, Specifically, when immunosuppressive therapies have a poor response. Combined steroid and d-penicillamine therapy could be successful in this situation[6]. Autoimmune hepatitis has an emerging complexity that has posed many diagnostic and management challenges[7].These challenges present difficulties in understanding the many clinical phenotypes, improving current corticosteroid regimens, detecting depressed patients early, integrating new treatment options into safe and efficient management strategies, and developing new therapies specific to molecular and cellular sites[7,8]. Acute non-viral hepatitis, acute-on-chronic liver failure and acute liver failure can be included in WD. WD, autoimmune hepatitis (AIH), liver damage (DILI) triggered by medication and indeterminate causes, drug-induced liver injury (DILI) and causes that are indefinite should be included in the differential diagnosis before the viral etiology of acute hepatitis has

been eliminated. WD has not historically been diagnosed in several WD patients who present with acute liver failure. The underlying, but unrecognized, cirrhosis is usually present. In addition to the conclusive characteristics of acute I-phosphatase, Classic Wilsonian Acute Liver Failure (ALF-WD)-Coombs-Classic Wilsonian Acute Liver Failure (ALF-WD)-Coombs-negative intravascular hemolysis, elevated serum copper and urinary copper excretion, moderate serum aminotransferase elevations compared to other etiologies of acute liver failure, and subnormal serum alkaline phosphatase are sometimes differentiated clinically in these patients. Any acute liver failure caused by WD is a medical emergency (as well as the classic Wilsonian acute liver failure). These patients should be relocated immediately to the liver transplantation and urgent liver transplantation management center[9]. Acute-on-chronic liver failure precipitated by infection, hypotension, or acute worsening of WD is a risk in patients with pre-existing serious liver damage caused by WD. Acute hepatic or acute-on-chronic liver failure is a risk for patients who have declined medically-advised WD care.

Case Presentation

In the Rare Diseases Clinic in AL-Imamen AL-kadhemaiin medical hospital/Iraq-Baghdad, (June-2015), a case of a 14-year-old (wt.26 kg.) female patient has been reported as Acute Hepatitis with a negative prior history of any other diseases but due to G6PD deficiency for a blood transfusion at age 5-years old. Patient lab data: ALT. (78 U/L), AST (100 U/L), ALP (420 U/L), TSB. (105 mg/dl.), Bilirubin (78.8 mg/dl) (Jaundice), INR.(0.9 sec.), Ceruloplasmin (17.9 mg/dl.), U. copper (105 mcg/dl.), U. copper/24hr.(1580 mg/dl.) and No Kayser-Fleischer (KF) ring. Patient start on Penicillamine full dose, but continue to have increase in

Bilirubin and liver transaminases levels. After three months on Penicillamine (250 mg *2) meanwhile, she developed Tea colored urine, normal HBC and her liver enzymes improved in Oct.2015. Until Dec.2015, her lab data were normal as : ALT (55 U/L), AST (47 U/L) and ALP (255 U/L). So, she was shifted to zinc Sulfate 150mg/D, due to absence of Zinc Acetate (not available at the hospital and the market). In July.2016, U.copper varied from (32 to 84 mcg/dl.), there was another exacerbation of hepatitis by double elevation of transaminases and ALP (486 U/L) (remarkable elevation). So, she was resumed on Penicillamine to 1000mg/D divided in two daily doses, U.copper 945mcg/dl.), which indicate Zinc Sulfate failure. On Sep.2016, Renal function tests were normal, Transaminases normalized, ALP(404 U/L) (more than 4 times upper the limit) so, she was on Penicillamine + B6 assuming it's a sort of Cholangitis). Early in 2017, patient shifted to Zinc Sulfate (150 mg/D), U. copper below (60 mcg/dl.) In April 2017, Zinc Acetate started (150mg*2), U. copper (64mcg/dl.) & ALP continue on a high level. July 2017: TSB. (1.44 mg/dl.), ALT (406 U/L), ALP (625 U/L), U.copper(58 mcg/dl.) Aug.2017: ALT (55 U/L), ALP(472 U/L), Lkm (+ve), Gamma Protein (159 g/L) mild elevation and U. copper (120 mcg/dl.). She was doing well on Zinc Acetate. In 2018: U.copper (88 mcg/dl.), Gamma Globuline(19.7 g/L.), Liver Kidney Microsomes(LKM.) (+ ve).

Patient stop the treatment:

March 2018: Gamma Globulin(21 g/L.), U. copper (172 mcg/dl.), s. copper (9 mcg/dl.), ALP (237 U/L), ALT (78 U/L).

Patient maintained on Zinc Acetate.

Aug.2019, patient started:

Prednisolone (5 mg.)	Azathioprine (50 mg.)	Zinc Acetate (150 mg /D.)
1*3 for 1 week	1*1	1*1
1*2 for 1 week		
1*1 for 1 week		

On Feb.2020:

Patient on Azathioprine (50mg/D) and Zinc Acetate (150mg/ D):

-U.copper.24hr.(34 mg/dl), ALT(73 U/L), AST (77 U/L), ALP (347 U/L) and the Fibro scan demonstrate stage 4 (F4): advanced liver scarring (cirrhosis).

Markers	On admission	After three months of Azathioprine and Zinc Acetate	Reference values
Alanin transaminase (ALT.)	100	73	10-49 U/L
Aspartate transaminase (AST.)	87	77	<34 U/L
Alkaline phosphatase (ALP.)	420	347	46-116 U/L
Gamma globuline (GGT.)	15.9	19.7	<15 g/L.
Bilirubin	2.9	1.4	<1.3 mg/dl.
Urinary copper per day (U. Copper /D)	105	38	<40 mg/dl.
S. Ceruloplasmine	17.9	23	22-58 mg/dl.
International normalized ratio(INR.)	0.9	-	<1.2 sec.
Liver kidney microsome (LKM.)	+ ve /post 2years.	+ ve.	
Immunoglobulin G (IgG.)	11.8	13.5	7-16 mg/dl.

Table 1: Laboratory findings for the patients on admission versus three months of treatment with Azathioprine and Zinc acetate.



Discussion

Wilson Disease is a serious disease that can conduct to multiple hepatic outcomes, including active chronic hepatitis. Owing to the absence or malfunction of P-type ATPase ATP7B transporting copper, its etiology relies on the defective incorporation of copper into apo ceruloplasmin. Symptoms differ, usually either hepatic or neurological at the time of diagnosis, depending on the main affected organs. The epidemiological profile consists of patients between the ages of 5 and 35, although there have been records of younger and older cases. Low ceruloplasmin levels are seen in most patients with neurologic WD, but about half of Wilson's patients with liver disease may be outside the normal range[10]. The presence of Kayser-Fleischer rings is found at diagnosis in about 50 percent of cases[11]. Also, the elevation of urinary copper considered as an effective marker of diagnosis. When the etiology is still uncertain, liver biopsy is considered. AIH, on the other hand, is a chronic disease causing progressive destruction of liver parenchyma. The pathological mechanism is still unclear, and cirrhosis normally results without appropriate care[12]. The AIH diagnostic criteria are the presence of autoantibodies, hyper gamma globulinaemia, Aminotransferase and negative viral marker elevation. Unlike WD, AIH patients typically respond well to immune suppressor therapy, which precludes liver transplantation [13]. In literature, a few instances of similarities have been identified between these two diseases. Cases of WD and positive autoantibodies of two patients with liver disease have been documented by Milkiewicz et al. In their research, patients had a partial initial response to prednisolone therapy [14], unlike our case. Dara et al also mentioned a case where both AIH and WD characteristics were present. Their patient reached the scores for these diseases and was treated for all of them with a positive answer (azathioprine, prednisolone and d-penicillamine)[15]. AIH markers were also reported for acute hepatitis caused by WD, with generally bad results associated with delay in diagnosis. The role of autoantibodies in WD is still unknown; due to hepatocyte necrosis or even a concurrent display of both entities, it may be an early feature of its pathological process[16,17]. For this reason, when faced with insufficient response to initial therapy, assessing AIH patients for WD can be life-saving[18]. In conclusion, whether it is due to primary Auto Immune Hepatitis and Wilson disease or Pencillamine sensitivity, further

investigations are required. Lack of adherence was obvious especially when the patients start Zinc sulfate on Dec.2015. Due to Gastro intestinal side effects, poor adherence from the parents sides, especially a remarkable elevations in ALP levels was noticed and lead to Hepatitis exacerbations. When starting chelation therapy (D-penicillamine) on July 2016, there was a minimum decrease in ALP levels and cholangitis were observed. During 2017, patient start Zinc Acetate, she was doing well. Later in 2018, there was a significant worsening in ALP levels and increase in the Gamma globuline levels and LKM (+ve). Patient started Prednisolone (5 mg.), Azathioprine (50 mg.) Zinc Acetate (150 mg /D.) later on 2019, a cirrhosis were shown on Feb.2020. Patients non adherent on medications or dietary copper contents leads to worsening in clinical presentations and even death. Therefore, adherence has an extremely important role for the long-term success of treatment. Failure to adhere to lifelong therapy can lead to substantial progression of WD-associated liver disease and/or liver failure, the latter requiring liver transplantation. A significant clinical appearance closely resembles autoimmune hepatitis, children, but also young adults, in particular (AIH). This is a chronic inflammatory liver disease characterized by increased serum aminotransferases, hyper gammaglobulinemia, non-specific involvement of autoantibodies (microsomal antibody of the liver kidney, LKM, anti-nuclear antibody, ANA; smooth muscle antibody, SMA;), hepatitis interface histology, and immunosuppression response[19]. As there is no single pathognomonic function, a rating system that has been revised and modified allows the diagnosis of AIH. Classic AIH can have a chronic or acute appearance[20,21]. Significantly, WD's obvious simple acute hepatitis proved to be close to acute autoimmune hepatitis. Several studies record a pediatric WD clinical appearance close to that of AIH[25-28,29,30]. Because of the early cases of WD that clinically mimic autoimmune hepatitis[22-24]. In others, WD was misdiagnosed as AIH, and treated, albeit inadequately, as AIH. For example, in adult girls, an 8-month history of jaundice, ascites, hyperglobulinemia, positive ANA, hepatitis device, and liver biopsy cirrhosis demonstrated improvement in corticosteroid therapy. But WD screening findings a month later showed positive results with low serum ceruloplasmin, increased urinary copper and 385 µg/g dry weight liver copper. D-penicillamine was initiated and corticosteroids, she becomes clinically stable and tapered off [25]. ANA-

positivity (type 1 AIH) is more common than LKM-positivity (type 2 AIH) in AIH-like WD, but this latter pattern may occur. Since acute liver failure due to AIH can be difficult to diagnose, acute liver failure presents major diagnostic problems. A similarly non-descriptive clinical picture of acute liver failure may be present in pediatric patients with WD, not the traditional ALF-WD picture. Initially, a 17-year-old girl with acute liver failure initiated a corticosteroid investigation focused on clinical and histological features of AIH in the midst of widespread IgG and negative autoantibodies. Clinical decline was responsible for urgent liver transplantation. Explant histopathology was consistent with WD; baseline 24-hour urinary copper excretion was diagnosed with 10,322 µg/24 hours (162.6 µmol/24 hours) of urinary copper, with findings available only after transplantation[28]. There was a liver biopsy. A 15-year-old girl with acute liver failure had ANA 1:320, SMA 1:160, hyper gamma globulinemia, and plasma cell infiltration, but she also had low serum ceruloplasmin, Kayser Fleischer rings, and high concentrations of liver copper. She started off with both penicillamine and corticosteroids, but as her condition progressed, she underwent liver transplantation. She had WD, confirmed genetically[31]. Another problem is that, as a consequence, some people with WD might get autoimmune hepatitis. In such cases, the disease mechanism may be similar to the situation in which a person with pre symptomatic WD experiences acute liver failure due to an inter current viral infection[32]. The affected individual develops AIH in this rare case. Possibly, but not certainly, due to damage to the hepatocellular plasma membrane caused by copper. In children with WD with prominent autoimmune traits, ulcerative colitis can occur[19,32]; however, patients on chelating (Trientine) has also been reported as an adverse occurrence. Some children have a genetic makeup that may be associated with ATP7B mutations and that predisposes them to autoimmune disease. In any case, the presence of each disease needs to be completely identified or denied[33]. Diagnostic complications may be primary sclerosing cholangitis (Roberts EA, unpublished observations) or, in particular, autoimmune sclerosing cholangitis (ASC), as stainless copper is used in liver biopsies[34]. In these conditions and WD, the copper distribution pattern in the liver seems to be distinct.

Conclusion

The presence of autoimmune liver disease and Wilson's disease is considered as uncommon entity. The problem in diagnosing is that, clinicians should have a high degree of suspicion. A high degree of understanding and knowledge is required for this situation. Therefore, it is prudent to recognize this form of hepatitis at the same time in rare patients with dominant disease features and to initiate medical treatment for both of them.

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