Case Report

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Wilson's disease along with non-alcoholic steatohepatitis, autoimmune and chronic viral hepatitis C - a case report

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Abstract

Wilson's disease is an inherited disease with disordered copper metabolism. Numerous clinical manifestations masking various other diseases are known. We report a case of a patient with a coexistence of several liver diseases such as Wilson's disease, non-alcoholic steatohepatitis, autoimmune hepatitis and viral hepatitis C, which are diagnosed and treated consecutively in the course of their clinical manifestation. In our modest opinion, this is the first description of this combination in the literature available.

Keywords: Wilson's disease, non-alcoholic steatohepatitis, autoimmune hepatitis, viral hepatitis C, treatment

Introduction

Wilson's disease (WD) is a rare genetic disease. It is characterized by the accumulation of copper in various organs, mainly in the liver, brain, and kidneys. This is due to a defect in the ATP7B gene leading to reduced copper-transporting protein ceruloplasmin formation, the low level of which causes copper deposition in various tissues. The disease presents itself with symptoms from various organs and systems (1, 2). Its coexistence with other diseases must be taken into consideration (3). It is necessary to include WD in liver screening in any cases of elevated aminotransferase (AT) concentrations, hepatosplenomegaly, hepatic steatosis and cirrhosis, in the presence of other etiological factors as well as in patients at any age.

Clinical case report

Here we present a 49-year-old man who, at the age of 35 years, was hospitalized for AT elevation in 2007. The additional tests revealed the presence of several positive autoantibodies such as ANA (++), AMA (+), antibodies to hepatitis C (HCV), with viral load of 2370000 IU/mL and 1+3 genotype. Ultrasound examination showed a moderate hepatic steatosis. At that time, the patient was of normal body weight (body mass index, BMI of 24.5 kg/m2), newly-diagnosed diabetes mellitus (DM), and arterial hypertension (AH). Liver biopsy proved fatty degeneration with microvesicular and macrovesicular steatosis and liver fibrosis of third degree (F3), without any hemosiderin deposition. A one-year treatment with pegylated interferon and ribavirin was performed resulting in almost AT normalization and permanent HCV-RNA negativity. However, hypothyroidism developed during the treatment. In the course of the follow-up, a new increase in liver blood tests was established. Given the positive autoantibodies found out in previous hospitalizations, the hypothesis of autoimmune hepatitis was accepted and in March 2011, treatment with Budesonide in a dosis of 9 mg daily was started. The tests of the copper metabolism examined for the first time demonstrated significant abnormalities such as low ceruloplasmin, high spontaneous and provoked 24-hour urine copper excretion (1.6 μmol/24 hours and 20.5 μmol/24 hours, respectively). In June 2011, a second liver biopsy showed evidence of disease progression manifested by predominant macrovesicular steatosis, advanced fibrosis, and signs of liver cirrhosis.

Table 1. Dynamics of laboratory and instrumental tests

	ANA AMA	HCV-RNA (1+3)	ALT	AST	GGT	Cp	Urine Copper spont/prov	FibroScan		
								E (kPa)	CAP (dB/m)	
2007	(++)	2370000	241..182		122					biopsy
2008			178	108	66					
May 2008 – May 2009 – PEG interferon+Ribavirin										
03.2009		(-)								
12.2010		(-)	104	44	48	0,13				
03.2011	(+)	(-)	105	47	48	0,17	1,6/20,5			
April 2011 – December 2011 – Budesonide 9 mg/day										biopsy
06.2011	(-)		64	33	39					
03.2012	(-)		49	28	27		1,8/33,6			
Recommendation for chelation treatment with D-penicillamine										
11.2012		91	43			0,19	1,6/39,6			
December 2012 – start of D-penicillamine treatment										
03.2018							9,6	12	352	
06.2021	(-)	(-)	40	29	31		7,7	10,3	306	

HCV-RNA – IU/ml; AST ALT, GGT – IU/L; Cp – ceruloplasmin - g/L; spont – spontaneous; prov - provoked
Urine copper - μmol/24 h; E – elasticity; CAP - Controlled Attenuation Parameter

Budesonide treatment was discontinued after nine months due to persistently elevated AT and negative autoantibodies as well. The repeated diagnostic search included WD because of the significantly increased

24-hour spontaneous and provoked urinary copper excretion (1.6 μmol/24 hours and 39.6 μmol/24 hours, respectively). A revision of the second biopsy was performed consisting in rhodanine staining in order to detect copper in the liver parenchyma indicated the presence of fine yellow-brown intracytoplasmic granules in the hepatocytes. Kaiser-Fleischer ring and neurological symptoms were missing and DNA analysis did not identify the most common mutations at all. According to the Leipzig Score system for WD diagnosis, the patient scored 4 points, which established the definite diagnosis. Due to personal reasons, chelation treatment was postponed. In December 2012, treatment was started with D-penicillamine as a copper chelator. Following this therapy, liver parameters returned to normal and an effective copper excretion was observed (Table 1).

During the follow-up, the patient gained body weight (BMI of 32.5 kg/m2). He did not consume any alcohol. The liver density measured with transient elastography, FibroScan, showed high-grade F4 fibrosis (12 kPa) in 2018, with a tendency to a slight decrease down to 10.3 kPa (June 2021) (Fig. 1).

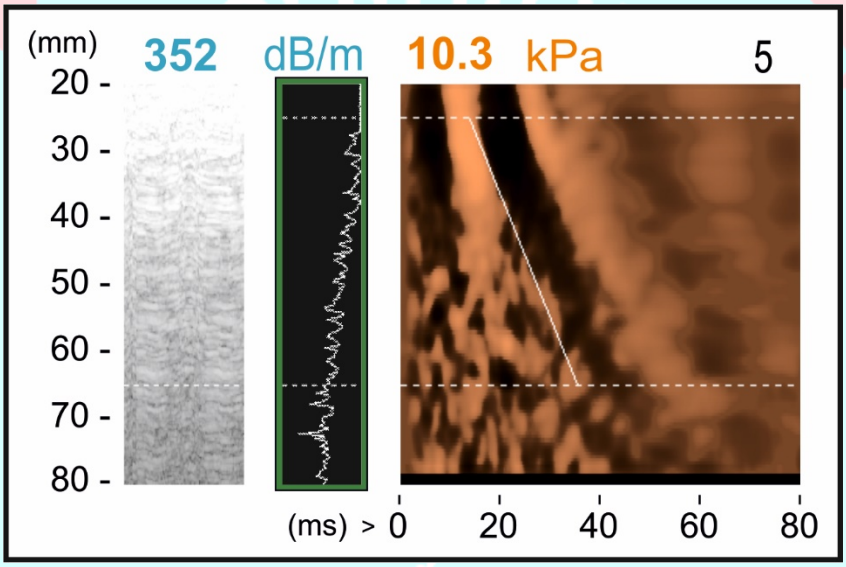

Fig. 1. FibroScan image

Discussion

Non-alcoholic fatty liver disease (NAFLD) is a significant health problem and represents the hepatic manifestation of the metabolic syndrome (4). Our patient has a metabolic syndrome developed during the clinical observation consisting of obesity, diabetes mellitus (DM), AH, and mild dyslipidemia (cholesterol of 5.65 mmol/L). Elevated blood liver tests of AT require a complete liver screening. The virological examination reveals active viral hepatitis C, successfully cured with the standard antiviral therapy at that time (5). It is known that autoantibodies can also be positive in WD, although in low titres, as an autoimmune phenomenon, in contrast to the significantly higher titres established in our patient. Their complete negative values after Budesonide treatment prove the autoimmune disease.

After persistent healing of the HCV infection, negative autoantibodies, and mild AT activity, complete liver screening is required again, resulting in WD diagnosis. The patient's liver disease has a combined etiology

- WD, viral and autoimmune hepatitis and metabolic syndrome (DM, AH and obesity) with nonalcoholic steatohepatitis (NASH). Histological changes are most likely due to a complex hepatic injury - steatosis - present both in DM and as the first and common morphological finding of WD (6, 7). Fibrosis is a sign of advanced liver disease as a result of NASH, with the involvement of hepatocytolysis due to an autoimmune and HCV infection and copper accumulation, too (8). It is noteworthy that the absence of Kaiser Fleischer ring is observed in about 50-60% of the cases with a hepatic form of WD. In addition, the absence of the most common mutations also does not rule out this disease. More than 800 mutations in WD have already been described (9).

The patient received recommendations for diet and physical exercise. Due to fluctuating slightly elevated AT and given the data on metabolic syndrome such as overweight, DM and mild dyslipidemia, we assume that NASH, superimposed on the disturbed copper metabolism contributes to the development of fibrosis and transition to liver cirrhosis according to morphological data (10). The registered liver density decrease measured by transient elastography is, probably, due to a good DM control, a slight body weight reduction (during the period between 2018 and 2021) as well as to a continuous chelation therapy (11). No signs of liver disease progression are established at all.

Cases of combination of WD with autoimmune hepatitis (5, 8, 12), with viral hepatitis C and B (13) and with NASH (14) have been described in the literature available. We failed to find a case description with the existence of such a combined liver pathology as in our patient. The autoimmune hepatitis is in permanent remission and there is sustained negative HCV-RNA in this patient.

Conclusion

Knowledge of the clinical features of the hereditary and metabolic diseases encourages the clinician to perform purposeful diagnostic search. WD should be considered in all the cases of unclear liver disease. The presence of one certain etiological factor does not exclude the presence of other competitive causes of chronic liver disease. Good knowledge of WD clinical diversity will help in the applying of extensive screening and diagnosis of this disease in patients with concomitant liver pathology. Continuous lifelong chelation treatment warrants a stable liver function and reduces the risk of progression and decompensation. Properly treated patients have a favourable long-term prognosis.

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