THE "MIMIC" LIVER DISEASE IN WILSON'S DISEASE

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Rezumat

Afecțiuni hepatice mimate de boala Wilson

Boala Wilson este o maladie determinată genetic rară ca prevalență, dar şi rar diagnosticată de specialişti prin insuficienta recunoaştere a acestei maladii, precum şi prin mimarea altor afecțiuni hepatice în cadrul acestei boli genetice.

Deseori, hepatita autoimună sau steatohepatita nealcoolică este confundată cu boala Wilson, prin tablou clinic asemănător, precum şi prin teste de diagnostic care de asemenea se pot modifica în aceste patologii (reducerea ceruloplasminei, sporirea cuprului în urină pot fi întâlnite şi în alte afecțiuni hepatice decât în boala Wilson).

Odată suspectată, boala Wilson necesită să fie confirmată prin testul genetic (mutațiile din cadrul genei ATP7B) sau prin biopsie hepatică cu examen histochimic.

Cuvinte-cheie: *boala Wilson, afecțiuni hepatice mimate, test genetic, biopsie hepatică*

Резюме

Мимические заболевания печени при болезни Вильсона

Болезнь Вильсона относится к редким заболеваниям. Картина хронического гепатита при болезни Вильсона схожа с клинической картиной других нозологических форм гепатита, что требует исключения болезни Вильсона у всех больных с хроническим гепатитом, особенно у молодых больных и в случаях сочетания поражения печени с неврологической симптоматикой.

Диагноз подтверждается низкой концентрацией церулоплазмина в сыворотке и увеличением суточной экскреции меди с мочой, которые возможны также при других заболеваниях печени (аутоиммунный гепатит, хронические активные заболевания печени, холестаз, острая печеночная недостаточность другого генеза), у некоторых гетерозиготных носителей мутации болезни Вильсона.

Несомненно, генетические тесты способны точно подтвердить диагноз, однако, учитывая генетическую вариантность, исследование становится необоснованным с экономической позиции.

Ключевые слова: *болезнь Вильсона, мимические заболевания печени, генетический тест, биопсия*

Introduction

Wilson's disease is listed as a "rare disease" by the Office of Rare Diseases of the National Institutes of Health. Worldwide, the incidence of Wilson's disease is 10-30 million cases, and the heterozygote carrier rate is 1 case per 100 persons, with the genetic mutation frequency varying from 0.3-0.7%. The prevalence of Wilson disease is 1 per 30,000 individuals. In general, the upper age limit for considering Wilson's disease is 40 years and the lower age limit is 5 years, although the disorder has been detected in children younger than 3 years and in adults older than 70 years [1].

Since the copper accumulation occurs in the liver initially, the disease often starts with hepatic symptoms; therefore, during childhood and the teenage years it is the most common manifestation. The liver involvement may range from *mild hepatitis, fulminate hepatic failure to chronic hepatitis and cirrhosis* [2].

Clinical peculiarities in Wilson disease

- One fourth of all Wilson patients experienced sometime in their lives an acute episode of hepatitis, presenting with non-specific symptoms (malaise, anorexia, epigastric pain, jaundice, elevated LFT) without viral markers or history of a toxic agent [1, 3].
- It is important to rule out Wilson disease in cases with non- viral acute hepatitis, especially if mild hemolysis and low uric acid level are also present.
- Fulminate hepatitis is a relatively rare, severe disease, which is often lethal. It usually occurs during the teenage years or young adulthood with symptoms of rapidly progressing acute hepatitis (deep icterus, encephalopathy, bleeding disorders, terminal renal failure, hepatic coma [5].
- Chronic hepatitis is the most common liver pathology in WD.
- The liver biopsy specimen reveals non-specific changes of chronic inflammation, intranuclear glycogen and periportal steatosis. The staining of the copper associated protein is usually positive. Measurement of the hepatic copper content aids in establishing the definitive diagnosis.

The recognition of Wilson disease is often the process of exclusion of more common causes (e.g., viruses, alcohol, autoimmunity), it is important to emphasize that awareness of the clinical features of these metabolic liver diseases should promote a proactive diagnostic evaluation [1, 6].

Table 1

Differential diagnoses of Wilson disease in patients with hepatic manifestation

Condition	*Differentiating signs/ symptoms*	*Differentiating tests*
Viral hepatitis B, C	Patients with viral hepatitis may have a history of a febrile illness or blood transfusion, but otherwise the symptoms and signs may be identical.	Serological marchers for HBV or HCV
Haemochromatosis	Patients with haemochromatosis may present with other features such as diabetes, skin pigmentation, arthritis, impotence in males, and cardiac enlargement with or without symptoms and signs of heart failure.	Iron parameters and liver biopsy are diagnostic.
Alpha-1 antitrypsin deficiency	Patients with alpha-1 antitrypsin deficiency may have chronic lung disease such as emphysema occurring earlier than expected (in the 40- to 50-year-old age group) as well as liver disease.	Tests show that enzyme is deficient
Autoimmune hepatitis	Patients may have other associated autoimmune conditions and will respond to steroid therapy. However, Wilson's disease should be excluded before this diagnosis is assumed	Patients may have a positive autoantibody screen including ANA, ASMA, anti-LKM and others.
Steatohepatitis	Patients with steatohepatitis tend to be obese with clinical features of hepatitis. Wilson's disease should be excluded before this diagnosis is assumed	Fatty liver and inflammation on biopsy.
Alcoholic cirrhosis	Patients may have a history and signs of alcohol excess. Wilson's disease should be excluded before this diagnosis is assumed, even if the patient drinks.	None.
Haemolytic anaemia	If hepatic bouts are severe in Wilson's disease then haemolysis may occur. Haemolysis in the presence of liver disease in a person aged <40 years should prompt testing for Wilson's disease	Tests for alternative causes of haemolytic anaemia, including Coombs antibody, Hb electrophoresis for HbS, and autoantibody screening for autoimmune diseases.

Masks from other liver disease in Wilson disease

The clinical presentations of Wilson's disease can mimic other liver disease: autoimmune hepatitis (especially in younger patients), nonalcoholic fatty liver disease, acute hepatic failure [3, 4].

• Patients in the pediatric age bracket who present a clinical picture of autoimmune hepatitis should be investigated for WD.

• Adult patients with atypical autoimmune hepatitis or who respond poorly to standard corticosteroid therapy should also be investigated for WD.

• WD should be considered in the differential diagnosis of patients presenting with nonalcoholic fatty liver disease or who have pathologic findings of nonalcoholic steatohepatitis.

• WD should be suspected in any patient presenting with acute hepatic failure with Coombs-negative intravascular hemolysis, modest elevations in serum aminotransferases, or low serum alkaline phosphatase and ratio of alkaline.

The differentiation of Wilson's disease from autoimmune hepatitis (AIH) can be supported by the presence of a Kayser -Fleischer ring and through urine and serum copper studies in patients with Wilson's disease. Because the onset of fulminant hepatic failure (FHF) may be the first presentation of Wilson's disease (WD) and autoimmune hepatitis (AIH) in previously asymptomatic adolescents, determination of the etiology of FHF is critical as treatment and prognosis differ between these two entities. Patients with AIH may be salvaged by medical treatment. On the contrary, liver transplantation is currently the only lifesaving therapeutic option available for patients with WD who present with fulminant liver failure. To establish the diagnosis of WD and AIH in the setting of FHF remains challenging for diagnosticians and decisions regarding liver transplantation may be necessary before a diagnosis is firmly established [3, 5].

Differential diagnosis of NASH is important, and led to the confirmation of Wilson's disease. Patients with NASH often present with few or no symptoms, though imaging techniques and liver biopsy show fat accumulation in the liver, mostly accompanied by hyperlipidemia. However, evaluation of patients based on fatty liver, hyperlipidemia, and abnormal liver function tests may not be sufficient in detecting the severity of the underlying cause. Therefore, for the adult and even elderly patients with unexplained histologic findings of steatohepatitis, it is reasonable to consider the possibility of Wilson's disease, before starting any treatment regimen [1, 4].

Laboratory diagnosis

• Classically, serum ceruloplasmin concentrations are very low in parallel with low serum copper levels. Though serum ceruloplasmin estimation alone is not specific enough to diagnose Wilson's disease, concentrations as low as in this case are unusual for any other diagnosis. Ceruloplasmin synthesis can be modestly reduced in decompensated liver disease of any etiology or in acute liver failure. Protein losing enteropathy, nephrotic syndrome, and malnutrition will also reduce serum concentrations. Conversely, as its synthesis can be stimulated by estrogens and it is an acute phase reactant, patients taking oral

contraceptives or those with acute inflammatory change within the liver may have normal serum levels [2, 3].

• A 24 hour copper estimation is a simple and useful confirmatory test with raised values (>100 µg/24 hours) invariably seen in symptomatic WD. Concentrations in this case were greatly raised.

• A liver biopsy, in itself, may not be diagnostic but is helpful in determining the extent of hepatic involvement and whether or not there is established fibrosis and moderate inflammatory change and copper accumulation in the hepatic tissue be consistent with Wilson's disease.

• The sequence analysis of ATP7B gene (WD gene) to identify the mutations is clinically available as a test. Although this is the most updated and thorough test, that some alterations such as large deletion or duplication may not be detected with this method. It is important that the biochemical testing must be performed prior to genetic tests [1, 4, 5].

Table 2

Modification the level of ceruloplasmin and urine cooper in liver disease

Level of ceruloplasmin can be decreased in:	*The 24 hours urine cooper can be increased in:*
Severe liver disease of any cause Wilson disease Heterozygote carriers from ATP7B Protein losing enteropathy Aceruloplasminemia Menke's disease Nutrition copper deficiency Proteinuria	Chronic active hepatitis Biliary primary cirrhosis Primary sclerosing cholangitis Autoimmune hepatitis Proteinuria Rheumatoid arthritis

Treatment

• The two main treatment options are chelation treatment with penicillamine or referral to a liver unit for consideration for orthotopic liver transplant (OLT).

• Chelation therapy is the treatment of choice in patients with compensated liver disease. The usual starting dose of D-penicillamine is 250 mg daily increasing over a period of a few weeks to an eventual maintenance dose of 1.5 g daily. Trientine is an alternative chelating agent which may be used in those unable to take penicilamine. Elemental zinc inhibits gastrointestinal copper absorption but its long term effectiveness is unproven. Success of therapy is judged by clinical improvement [3, 4].

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