

CASE REPORT

ACUTE GALLBLADDER HYDROPS AND ARTHRITIS: UNUSUAL INITIAL MANIFESTATIONS OF WILSON'S DISEASE (WD)

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Abstract: Wilson disease (WD) is an autosomal recessive disorder, in which copper is deposited in the liver, brain, cornea and kidneys. The clinical presentation is variable, with fully expressed disease manifesting cirrhosis, neurologic damage and Kayser-Fleischer (K-F) ring on the cornea.

A 24-year-old patient developed right upper quadrant pain with a palpable mass and a swelling of the right talocrural articulation. X-rays were uneventful, but the routine examination of hepatic enzymes discovered a 6–8 fold increase in SGPT, SGOT and AST. Antibodies for hepatitis B, C were normal, as well as the ANA, ANCA, antimyochondrial and anti-smooth muscle antibodies. Ultrasound of the abdomen revealed extremely dilated hepatic, cystic ducts as well as gallbladder. A large, oedematous gallbladder with yellow green bile was removed, the liver was found to be cirrhotic, but as the operative bleeding was abundant a biopsy was not done. Serum ceruloplasmin was low [0.160 g/l (normal 0.204–0.407)], serum copper 12.7 $\mu\text{mol/l}$ (11.0–24.4), transaminases: always very high, in the last months normal/slightly elevated. Urine copper: 1.0 $\mu\text{mol/24h}$ (> 9.44). As first seen the proband had tremor, dysarthria, dystonia and K-F ring on the cornea. After 10 months of treatment with penicillamine his transaminases normalized, the tremor, dysarthria, dystonia initially got worse and then ameliorated. The coagulation times are ameliorated, but not yet normalized. Mutational analysis has shown that the proband is homozygote for c.3207 C- > A, p.H1069Q while his parents are heterozygotes. His sister is a healthy non-carrier. In brief, we describe an unusual presentation of WD, with gallbladder hydrops and talocrural arthritis in a patient with complete clinical manifestations of the disease.

Key words: Wilson disease, Kayser-Fleischer rings, gallbladder hydrops. arthritis, p.H1069Q mutation.

Introduction

Wilson disease (WD) is an autosomal recessive disorder of copper metabolism. WD causes toxic accumulation of copper in the liver, brain, cornea and kidney. Progressive liver cirrhosis, neurologic impairment, and Kayser-Fleischer (K-F) rings and/or renal malfunction are the classical clinical presentations of WD [1, 2].

Prophylactic therapy in affected but presymptomatic patients can prevent the onset of symptoms [3]. Therefore, early diagnosis is essential. The standard clinical and biochemical tests and the liver biopsy for hepatic copper analysis may give false-positive results. In addition, those tests cannot be applied in presymptomatic diagnosis. Molecular diagnosis overcomes these limitations.

We here present a late diagnosis of WD in a young man with an unusual presentation of WD: gallbladder hydrops and talocrural arthritis, having all three major clinical presentations: cirrhosis, neurologic signs and K-F rings. In addition, this is the first Macedonian patient with a mutational diagnosis. Namely, the most common mutation of the in the ATP7B gene in the central European population c.3207 C- > A, p.H1069Q has been detected.

Case report

This 24-year-old patient developed a swelling of the right talocrural articulation and right upper quadrant pain with a palpable mass. Fever, vomiting and jaundice were not present. X-rays were uneventful, but the routine examination of hepatic enzymes discovered a 6–8 fold increase in SGPT, SGOT and AST. Antibodies for hepatitis B, C (HBsAg, HbeAg and antibodies to HCV antigens) were normal, as well as the anti-neutrophil cytoplasmic antibodies (ANCA), antimyochondrial, antiactin (anti smooth muscle), antinuclear (ANA), anti-liver-kidney antibodies. Ultrasound of the abdomen revealed hyperechogenic liver parenchyma and an extremely distended, echo-free gallbladder, with dilatation of the biliary tree (hepatic and cystic ducts). The gallbladder was surgically extracted (a large, oedematous gallbladder with yellow green bile), the liver was found cirrhotic, but as the operative bleeding was abundant a biopsy of the liver was not done. Serum ceruloplasmin was low [0.160 g/l (normal 0.204–0.407)], serum copper 12.7 $\mu\text{mol/l}$ (11.0–24.4), transaminasis: always very high, in the last months normal/slightly elevated. Urine copper: 1.0 $\mu\text{mol/24h}$ (> 9.44). Haemoglobin, erythrocytes, serum ferrum, creatinin and urea remained normal throughout the course of the disease. The proband had intention tremor, dysarthria and dystonia. Kayser-Fleischer ring on the cornea was also noted. After 10 months of treatment with penicillamine his transaminases normalized, the tre-

mor, dysarthria and dystonia initially worsened and then ameliorated. The coagulation times are ameliorated (near normal), but not fully normalized. In addition he receives alpha tocopherol, vitamin B, K, C. Mutational analysis has shown that the proband is homozygote for c.3207 C- > A, p.H1069Q while his parents are heterozygotes. His sister is a healthy non-carrier.

Discussion

The estimated WD frequency in the U.S. Caucasian population was found to be about 1 in 55, 000 births [4]. The prevalence in the European populations is estimated to be around 1 in 30,000, while a higher prevalence of WD (1 in 2,600) was found in the northeastern region of the island of Gran Canaria (Spain) [5]. The prevalence of WD was estimated to be 1 in 5,400 in Hong Kong Han Chinese [6]. In general, the worldwide prevalence of Wilson disease is estimated to be in the order of 30 per 1 million. This is the first description of WD with mutational analysis in Macedonia.

WD results in accumulation of copper in the liver and brain when a membrane-bound copper transporter, ATP7B, is defective. ATP7B is expressed in hepatic, brain and kidney cells, and a defect can lead to liver, neurological and renal damage in WND patients.

To date, there are approximately 380 probable disease-causing variants in the ATP7B gene [6–18]. The most common mutation in patients from Europe is H1069Q [19]. A 15-bp deletion in the 5-prime region is frequent in Sardinia. Some other mutations are found to be more frequent in certain populations: M645R is common in Spain, R778L in patients from eastern Asia. The common his1069-to-gln mutation accounted for 42% of all WD patients in the German series [20]. In the U.S. Caucasian population approximately one-third of WD mutations are his1069-to-gln [4]. The Macedonian patient of Serbian and Macedonian extraction also had his1069-to-gln mutation.

Presentation is variable with a broad range of age of onset and symptoms, and not all biochemical signs used in diagnosis are found in every patient. It is generally agreed that WD should be considered in any patient at any age presenting with unusual liver or neurological abnormalities. As KFR is present in 100% of patients with CNS manifestations of WD, slit-lamp assessment is mandatory. WD has been described in children, adolescents and in the older age group [21, 22].

It was suggested that there are at least 3 forms of WD [23]. The rare "atypical form", with heterozygotes showing about 50% of the normal level of ceruloplasmin, and a probable German-Mennonite derivation. The second "typi-

cal form" is the Slavic type with a late age of onset and predominantly neurologic manifestations, while the third "typical" form is the juvenile type, which occurs mostly in Western Europeans, has its onset before the age of 16 years and is often hepatic. Others have also observed the existence of neurological, hepatic, and the hepatoneurologic type of WD [24]. Fulminant hepatic failure has also been reported [25, 26]. Other ethnic differences have also been observed: Jewish patients with later onset and milder disease [27], while Arab patients had an earlier onset and more severe course [28].

Myocardial involvements in WD include increased thickness of the interventricular septum and left ventricular posterior wall, as well as cardiac arrhythmias [29, 30]. Polyneuropathy before developing more typical symptoms of WD was also reported [31]. Occasionally, hypercalciuria associated with WD was also found [32–34].

Osteoarthritis and chondrocalcinosis has been infrequently reported in WD, and was speculated to result from accumulation similar to the arthropathy of hemochromatosis [36]. Osteoarthritis as initial WD manifestation has not, to the best of our knowledge, so far been reported.

MRI scans show abnormalities of the basal ganglia, generalized cerebral atrophy, and white matter abnormalities in some WD patients, particularly at the dentatorubrothalamic, pontocerebellar, and corticospinal tracts [37]. Leukoencephalopathy was also reported [38].

Since our patient was found to have only low ceruloplasmin levels, while copper in serum and urine was normal, genetic analysis was particularly important. The mutational analysis confirmed the diagnosis, as well as the observation that patients homozygous for the his1069-to-gln mutation have an almost complete range of clinical presentations [20].

Wilson disease can be effectively treated [39]. Penicillamine in presymptomatic and symptomatic patients is effective. However, penicillamine may lead to adverse effects involving the immune system or connective tissue. Also, it can cause the onset of neurological disease or worsening of neurological manifestations in symptomatic patients (as happened with our patient) when used in the initial therapy. Because of its adverse effects in some patients it is necessary to replace the treatment with triethylene tetramine (TETA) [40].

Zinc has been developed as an effective and nontoxic therapy in WD that blocks the absorption of copper and increases copper excretion in the stool [41]. Tetrathiomolybdate has shown excellent efficacy in patients with Wilson disease who presented with neurologic manifestations [41–43]. The adverse effects include bone marrow suppression or aminotransferase elevations.

WD has been successfully treated with an orthotopic liver transplant [44, 45]. However, postoperative central pontine and extrapontine myelinolysis has been reported [46].

The outcome of the treatment is difficult to foresee. Although treatable, WD remains a challenge for treatment, with a still high mortality. In a series of 142 patients, there have been 30 deaths: the cumulative probability of survival over a 15-year period was found to be 76.7 +/- 4.9% [47].

Our patient is so far being successfully treated with penicillamine. The neurologic manifestations are ameliorated, the hepatic enzymes normalized and the coagulation analysis ameliorated (near normalized). In conclusion, we present a young man of 24 years with initial WD manifestations of gallbladder hydrops and arthritis. To the best of our knowledge those initial WD manifestations have not so far been described.

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Резиме

**АКУТЕН ХИДРОПС НА ЖОЛЧНОТО КЕСЕ И АРТРИТ
КАКО НЕВООБИЧАЕНИ МАНИФЕСТАЦИИ
НА БОЛЕСТА НА ВИЛСОН**

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Апстракт: Болеста на Вилсон е автосомно рецесивно нарушување кај кое бакарот се депонира во црниот дроб, мозокот, корените, бубрезите.

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Клиничките манифестации се варијабилни и вклучуваат цироза, невролошки оштетувања и карактеристичен Кајзер-Флајшеров прстен на рочиците. Прикажаниот 24-годишен пациент иницијално се здобил со болка во горниот stomачен квадрант и палпабилна маса под десниот ребрен лак, како и болки во талокруралниот зглоб. Хепаталните ензими беа покачени 6–8 пати. Антителата за хепатит Б и Ц, АНА, АНКА, антимиохондријалните антитела и анти глатко мускулните антитела беа со нормални вредности. Ехосонографски беа најдени екстремно дилатирани хепатичниот, цистичниот дуктус, како и жолчното кесе. Со хируршка интервенција беше отстранета голема, отечена жолчна кеса со жолто-зелена жолчка. Црниот дроб беше циротичен што доведе до значително оперативно крвавење кое оневозможи интраоперативна црнодробна биопсија. Серумскиот церулоплазмин беше низок [0,160 g/l (normal 0,204–0,407)], серумскиот бакар нормален 12,7 $\mu\text{mol/l}$ (11,0–24,4). Бакарот во урината низок: 1,0 $\mu\text{mol/24 h}$ (> 9,44). При првиот преглед пациентот имаше премор, дизартрија, дистонија и К-Ф прстен на рожницата. По 10-месечно лекување со пенициламин неговите трансaminaзи се нормализираа, а коагулационите вредности се подобрија. Мутационата анализа кај пациентот покажа дека е хомозигот за мутацијата c.3207 C-> A, p.H1069Q, додека неговите родители се покажаа хетерозиготи. Неговата сестра е здрава и не е носител на мутацијатата. Накусо опишуваме невообичаена презентација на болеста на Вилсон со хидропс на жолчното кесе, талокрурален артрит, некомплетни биохемиски манифестации, но комплетна карактеристична слика на болеста.

Клучни зборови: Вилсонова болест, Кајзер-Флајшеров прстен, хидропс на жолчното кесе, артрит, мутација, p.H1069Q.

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