Wilson’s disease: a proposito of two clinical cases
Sara Drumond Freitas, Helena Sarmento, Glória Alves, Jorge Cotter

Abstract
Wilson’s disease is a rare disorder, with an autosomal recessive defect, caused by mutations in the ATP7B gene, a membrane-bound copper-transporting ATPase. Its deficiency results in the copper accumulation, preferably in the liver and brain.
Patients often present with hepatic (from asymptomatic elevation of liver enzyme to severe hepatic failure) involvement and/or neuropsychiatric disease. The diagnosis is based upon clinical, biochemical and histological findings. Because effective treatment is available, it’s important to make this diagnosis early, and prevent other manifestations.
The authors report 2 cases of Wilson’s disease with hepatic involvement, with distinct evolutions.
Key words: Wilson’s disease, diagnosis, treatment.

INTRODUCTION
Wilson’s disease (WD) is characterized by a genetic defect potentiating the toxic accumulation of intracellular copper.1 Its prevalence changes from 1/20,000 to 1/40,000, with a record of 1% of the population with ATP7B mutations.1,2,3 In Western countries, liver and/or neurologic manifestations emerge around the 2nd and 3rd decade of life. In India and Oriental countries, changes are earlier occurring at 4 and 5 years of age. The presentation age varies (4-60 years of age), with an average age of 21 years.1,4,5,6 It is thought that in such difference genetic factors may be implied (ability to produce antioxidant enzymes) and eating patterns (diet rich in copper: seafood, chocolate, walnuts, mushrooms, liver pâté).4,5

The clinical presentation is diverse being the classic form featured by patients from 5 to 40 years of age, with a decreased serum ceruloplasmin and the presence of Kayser-Fleischer rings.1,3 In children, the most frequent presentation is hepatitis, and the condition onset average age is from 10-13 years old. Around 45% patients present liver disease (increased transaminases; acute or chronic hepatitis; cirrhosis; hepatic disease complications – ascites, encephalo-}

pathy, upper digestive hemorrhage, and hypoalbuminemia), 35% neurologic involvement (Kayser-Fleischer rings; tremor; chorea; dysarthria; dysphagia) and 10% of psychiatric disturbances (depression; schizophrenia, psychosis). The remaining 10% may present hemolytic anemia, cardiomyopathy; arthritis, osteomalacia and hormonal dysfunctions.3,5,6

The screening of close relatives is recommended, as the early treatment in heterozygotic and/or asymptomatic patients may prevent the hepatic and neurologic lesions resulting of accumulating copper on the long term.1,3

CLINICAL CASE
1st Case: C.S.P.M, female gender, 18 years old, Caucasian, single, hairdresser, born and residing in Guimarães, with the following personal background: smoker 5-6 cig/day; tattooing and piercing for 5 months; use of oral contraceptive (OC) for 4 months; updated Vaccination National Plan (PNV); irrelevant gynecologic history; denied use of illegal drugs or risk sexual behavior.
She was admitted on the 31st July 2004 due an epigastralgia, burning sensation, recurrent, worsening with food intake (3 weeks of evolution), choluria and generalized pruritus (2 weeks of evolution), icteric sclerae and a weight loss of 5 kg in one week. She denied intake of mushroom, milk and non pasteurized dairy products or recent trips. In the objective exam she was aware, cooperating and oriented; with good color and hydration; icteric skin and sclera; no flapping; neurological exam without focal points; heart and pulmonary auscultation without changes; soft and depressible abdomen, painful to deep palpation.
in the epigastrium, no organomegaly, apyretic, normotensive and eupnoeic. Analytically the hemogram, clotting study and kidney function had no changes; TGO/TGP: 1807/3217 UI/L (N:10-31); total bilirubin: 8.69 mg/dl (N<1) and direct: 4.62 mg/dl (N<0.2).

During the 1st week, she kept epigastralgia and generalised pruritus. We got the following results: 1) Abdominal ultrasound “diffuse hyperechogenicity of portal spaces ... associated to hepatopathy. Diffuse thickening of the gall bladder wall”; 2) NEGATIVE Serology for A, B, C hepatitis, HIV, Cytomegalovirus, Epstein-Barr, Toxoplasmosis, Paul-Bunnell reaction; 3) NEGATIVE Autoimmunity (antinuclear antibodies, antiDNAds, antiSm, antiSSA/SSB, antimitochondrial, antiRNP, anti-smooth muscle, antiLKM); 4) NORMAL Proteinogram, ceruloplasmin, alfa1-antitripsin; 5) Iron kinetics: Transferrin Saturation=81%. An abdominal Nuclear Magnetic Resonance (NMR) with liver iron dosages was requested as well as keeping a daily analytical monitoring of the liver function and it was scheduled a hepatic biopsy.

On the second week, acholia started. Objectively, the test was overlapping. The abdominal NMR revealed “regular border liver, with increased dimensions, measuring around 18 cm in the median-clavicular line. Gallbladder with normal distention and parietal diffuse thickening. Liver iron dosage: 45 Mmol/kg (N<36)”. The liver biopsy has shown “acute hepatitis with multifocal necrosis and panlobular distress of the hepatocytes, with cholestasis, excluding viral etiology and pointing to a toxic/immune cause. Without a deposit of hemosiderin pigment” (Fig.1). We kept an expecting attitude requesting urinary copper dosage.

During the 3rd and 4th week the clinical condition was stable. The result of urinary copper has revealed 156 mcg/24h (<50). She was seen in Ophthalmology who visualized Kayser-Fleischer rings and a cerebral NMR (normal) was carried out. The diagnosis of Wilson disease was confirmed and penicillamine 900 mg/day and pyridoxine 25 mg/day were started. She was discharged on the 13th September 2004, referred to Internal Medicine outpatient service, with the normalization of the liver function (Fig.2 and 3). At present, she is asymptomatic and being medicated with Zinc 150 mg/day.

2nd Case: F.C.R.S, female gender, 27 years old, Caucasian, married, care assistant in a nursing home, born and residing in Fafe, with a personal history of kidney lithiasis, repeated tonsillitis, oral contraceptives for the last 10 months, updated vaccines (PNV), irrelevant gynecologist history; no drug or mushroom use and no recent trips abroad.

Since October 2004 she mentioned asthenia, anorexia and irritability. In mid November 2004 choluria started, increase on the abdominal perimeter, postprandial fullness, and worsening asthenia. By the end of November 2004, acholia had started, diffuse abdominal pain and food/biliary vomiting. On the 2nd December 2004 she was referred to the hospital due to “anemia + ascites + jaundice”. Objectively she was aware, cooperating and oriented; pale and dehydrated; skin and sclera jaundice; no flapping; neurologic exam without focus; heart and lung auscultation without changes; soft, not very depressible abdomen, with variable flank dullness; apyretic, normotensive and eupnoeic. Analytically: macrocytic anemia (Hb:7.4 g/dL; MCV:108 fL), negative Coombs test; liver dysfunction (total bilirubin:5.6 mg/dL – N<1 and direct:2.2 mg/dL – N<0.2; TGO/TGP>200 UI/L – N:10-31); Hypoalbuminaemia (alb:2.1 g/dL); Hypokalaemia (K+:2 mEq/L); Hypocalcaemia and Hypophosphataemia; increased prothrombin time (6 sec). A paracentesis was carried out and the ascitic fluid was suggestive of portal hypertension. During admission it was possible to get the following results:

1) NEGATIVE serology for Hepatitis A, B, C, HIV,
cytomegalovirus, Epstein-Barr, toxoplasmosis and Paul-Bunnel reaction;
2) NEGATIVE autoimmunity (antinuclear antibodies, antiDNA, antiSm, antiSSA/SSB, antimitochondrial, antiRNP, anti-smooth muscle);
3) NORMAL Alpha1-antitripsin and iron kinetic;
4) Ceruloplasmin: 7.1 mg/dL (N: 25-63);
5) Increased urinary copper;
6) Abdominal ultrasound “abundant fluid in the abdominal cavity, liver within normal dimensions”.

She was observed by the Ophthalmology with a description of Kayser-Fleischer rings. She was started in Penicillamine 900 mg/day.

On the 3rd day of admission there was a worsening of the clinical condition, with a C class in the Child-Pugh Classification (UNOS Status 3; MELD: 27). The Transplant Center was contacted and was transferred to Coimbra University Hospitals on the 6th December 2004. The patient has undergone liver transplant on January 2005 and died in the perisurgical period.

DISCUSSION

Before a clinical condition of acute hepatitis several diagnosis hypothesis should be raised, according to the age range, history and clinical suspicion. It is important to think about the infectious causes (Hepatitis A, B, C, D, E Virus; HIV; Cytomegalovirus; Epstein-Barr; Herpes simplex), alcohol consumption, metabolic/genetic diseases (Wilson’s disease, haematochromatosis, cystic fibrosis), systemic pathology (tuberculosis, sarcoidosis, amyloidosis), auto-immune etiology (auto-immune hepatitis, primary biliary cirrhosis, sclerosant cholangitis), consumption or exposure to toxics, among many other less frequent causes.1

Although Wilson Disease is a rare condition, it is often devaluated. In children and young adults, disease is often shown as fulminating hepatitis.1,3,4 The suspicion of Wilson’s Disease is raised before a condition of hemolytic anemia, negative Coombs test, associated to a coagulopathy resistant to vitamin K, rapidly progressive kidney failure and increase on transaminases (TGP>TGO). It is thought that viral infections and drugs are triggering factors for fulminating hepatitis in WD. The diagnosis of such clinical conditions require a high degree of clinical suspicion.1,3,4,7,8

The early diagnosis depends on the physical exam, ophthalmologic observation with slit lamp, liver function study and dosage of ceruloplasmin and serum and urinary copper. If any one of such endpoints is changed a hepatic biopsy with hepatic copper dosage should be carried out.1,4,7 The presence of Kayser-Fleischer rings is not WD specific and might be present in the primary biliary cirrhosis, chronic cholestatic disturbances and neonatal cholestasis. Usually it disappears and its reoccurrence raises the hypothesis of non-compliance to therapy.4,7,8

It is important to highlight that ceruloplasmin may be normal, because being a reactive protein in acute
stage, it is produced in excess in the inflammation. Other conditions can potentiate normal ceruloplasmin, such as pregnancy, oral contraceptives use or estrogen supplements. On the other hand, there are pathologies which contribute to low ceruloplasmin, from which the examples are the nephrotic syndrome, protein losing enteropathy, terminal chronic liver disease, viral acute hepatitis, toxic hepatitis, alcoholic steatosis hepatitis, aceruloplasminemia and Menkes’s disease. Serum copper is recommended for monitoring and not for diagnosing, as it is influenced by multiple variables, such as, the laboratory test used for its determination.

The urinary copper is used for the diagnosis (>100mcg/24h) and treatment monitoring. It should always be followed by dosing of urinary creatinine, for the evaluation of the sample reliability.

The liver biopsy with liver copper dosage is keeping the gold standard element in the diagnosis. The histology found is similar to the autoimmune hepatitis to the non-alcoholic liver steatosis, with fat infiltration in the hepatocytes, glycogen nuclear inclusions and portal fibrosis. Liver copper >250 mcg/g of dry weight of liver tissue is a WD diagnosis. However, a normal value does not exclude the disease, once the liver distribution of this one can be irregular in the presence of fibrosis or cirrhosis. The histology staining with rhodamine can be used, but it has a low sensitivity and its absence does not exclude WD. The histologic result should be supplementary to the reminded of the patient’s data.

The treatment is ad eternum and in a 1st state consists in removing the copper tissue, and posteriorly preventing its accumulation, through the use of chelating agents. Medical treatment is supplemented with dietetic recommendations, restricting the intake of food rich in copper (seafood, walnuts, dry fruits, peas, chocolate, cacao and mushrooms).

The therapeutic choice will depend on the way of the manifestation (Fig.4). In a mild hepatic form...
(increase on hepatic enzymes) it is started with zinc or trientine. In a moderate form (Score Nazer<9. Table I), is used zinc associated to trientine or penicillamine. In a severe form (Score Nazer>9) it should be referred to transplant. In the neuropsychiatric manifestation it is recommended tetrathiomolybdate associated to trientine and zinc. The maintenance therapy passes through the use of zinc or trientine (2nd line). With the appropriate treatment a recovery of the liver function occurs at the end of 1 year and the neuropsychiatric functions between the 6 and the 24 months.3,4,7,8

The WD has a fatal outcome if it is not treated. Symptomatic patients receive a long term treatment, once its withdrawal triggers the emergence of complications at the end of 9 months to 3 years. The prognosis, evaluated by Score Nazer, is worst in patients with an initial severe disease and an early age on the diagnosis.7,8,9

In conclusion we presented two clinical cases with distinct forms of presentation, which became a clinical challenge for the authors.

References