MINISTRY OF HEALTH OF THE REPUBLIC OF MOLDOVA

PUBLIC INSTITUTION
STATE UNIVERSITY OF MEDICAL AND PHARMACY
NICOLAE TESTEMITANU

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WILSON'S DISEASE.
"Self-assessment workbook"

Guidelines for students

Chisinau
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Department of Internal Medicine
Gastroenterology and Hepatology

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CONTENTS

PREFACE

This "Self-assessment workbook" on ***Wilson's disease*** is a collection of interesting cases of Wilson disease which cover the full range of pathology. Each case is presented as you will see it in a clinical situation where a patient presents a complaint or something is noted on examination or blood work. The question/ answer format will help one through the problem of making a diagnosis or in considering a differential diagnosis and also point to the best way to manage each condition.

Recognition of Wilson's disease is challenge number one facing Wilson's disease patients and their physicians today, and this book is designed to help students recognize the possible (or likely) diagnosis and help these patients.

Finally, after studying these guidelines we hope you will be able to:

- Recognize the Wilson's disease in a patient with unexplained liver disease;
- Describe the diagnosis, health consequences of Wilson's disease.
- Take an appropriate patient history (icluding medical, family and social), identify the physical findings associated with Wilson's disease.
- Describe the efficacy of pharmacologic approaches for the treatment of Wilson's disease

Wilson disease. *Self-assessment workbook* will come in handy for students, residents/fellows and internists interested in gastroenterology.

KEY POINTS

Wilson Disease is:

- Rare autosomal recessive disorder that causes excessive absorption of copper from the small intestine and decreased excretion of copper by the liver. The genetic defect, localized to arm 13q, has been shown to affect the copper-transporting adenosine triphosphatase (ATPase) gene (***ATP7B***) in the liver. The condition is characterized by excessive deposition of copper in the liver, brain, and other tissues.
- Clinicians should have WD in the differential diagnosis when patients under 50 years of age present with elevated liver enzymes, and/or parkinsonian symptoms, and/or behavioral changes. Therefore, it is necessary to screen for WD every patient under 50 with neurological disorder (dysarthria, tremor and other involuntary movements, dystonia, incoordination), hepatic disorders (hepatitis: viral negative acute or chronic; cirrhosis: any patient under 50 even with history of alcoholism or hepatitis C infection; hepatic failure), and behavioral disturbances (loss of ability to focus mentally on tasks, loss of control of emotions, depression, loss of inhibitions, insomnia, anxiety and psychotic manifestations).
- Many tests can be used to investigate patients who may have Wilson disease, including non–ceruloplasmin-bound copper (NCC; also called the "free copper" or copper index), 24-h urine copper, hepatic copper, and genetic mutation testing. Observation of KF rings in an ophthalmological examination further supports the diagnosis.
- The treatment paradigm for symptomatic patients remains copper removal with copper chelating agents; zinc is now increasingly used to maintain normal free serum copper levels in symptomatic patients who have undergone adequate chelation, and as first-line therapy in asymptomatic individuals to prevent copper accumulation.
- If patients adhere to lifelong maintenance therapy, the prognosis is generally good; in rare cases, including patients who present with acute liver failure or advanced end-stage liver disease unresponsive to medical therapy, liver transplantation is necessary and highly effective. A liver transplant reverses the underlying copper metabolic defect.

CASE ONE

Objectives:

1. **Indentify methods to appropriately diagnose Wilson disease.**
2. **Describe the clinical manifestations of specific Wilson disease.**
3. **Describe de diagnostic criteria and what investigations would confirm the diagnosis Wilson' disease.**
4. **Demonstrate the utility of presence of Kayser-Fleischer rings in Wilson disease.**
5. **Identify the treatment options for Wilson's disease.**

The patient was a 28 year-old male who had been experiencing a upper abdominal pain, nausea and increasing fatigue for the last several months. He also had noticed dark urine, jaundice and an 8 kg weight loss. The patient was admitted for work-up and treatment of his undiagnosed condition. His inpatient team was concerned about possible Wilson's disease and referred the patient to the ophthalmology clinic for evaluation of Kayser-Fleischer rings. He had no changes in vision or other ocular complaints.

A liver biopsy at age 13, performed after he was found to have abnormal routine labs prior to an apendectomy, showed fatty liver which was thought to be related to his weight. He had no additional follow up.

- **Past Ocular History**: None
- **Medical History**: The patient had a liver biopsy at age 13 with a diagnosis of fatty liver. He also had an apendectomy at age 13.
- **Medications**: None
- **Family History**: There is no family history of liver disease. The patient's father was an alcoholic.
- **Social History**: He reports heavy alcohol use (more than one five-pack of beer per day for over eight years). He smokes one pack of cigarettes per two day.
- **Review of Systems**: The patient reported an unintentional 8 kg weight loss. He had no mood changes, behavioral changes, or

movement disorders. Heart rate: 88 beats per minute (BPM); respiration: 18 BPM; blood pressure 130/80 mm Hg.

– **Ocular Exam**:

• Best corrected visual acuity: 20/20 OD and 20/20 OS.

• Pupils: 6 mm in dark, 3 mm in light.

• Anterior segment. Scleral icterus OU, 1-2 mm golden brown band seen at the limbus OU.

• DFE: normal discs, normal macula, periphery, and vessels OU.

The patient was admitted to the hospital for a diagnostic work-up as well as treatment for severe liver failure. Subsequent work up worsening liver function tests.

– He had normal serum ceruloplasmin and serum copper levels, but had an elevated urine copper of 189 ng/ml (normal is 12-80), and an elevated urine copper excretion of 1522 mcg/day (normal is 3-35) after penicillamine excretion test.

CASE QUESTIONS

1. **What is the likely diagnosis of Wilson's disease (WD)?**
2. **What additional information is important to obtain from a patient who present with these symptoms?**
3. **How is the test 24-urinary copper done?**
4. **What further investigations would confirm the diagnosis of Wilson's disease?**
5. **What treatment options might you consider and how would you manage this patient?**

CASE ANSWERS

What is the likely diagnosis?

• The low serum copper and ceruloplasmin concentrations or/ and elevated urine cooper and urine cooper excretion, in the setting of abnormal liver function, and hepatic manifestations (abdominal pain, jaundice, dark urine), body mass losing, fatigue may suspect Wilson disease.

• In this case the WD is suspected on unexplained liver disease at age 13 (confirmed liver biopsy) and the patient had an recent ophtalmological modifications like as KF ring, elevated urine copper of 189 ng/ml (normal is 12-80), and an elevated urine copper excretion of 1522 mcg/day (normal is 3-35) after penicillamine excretion test.

What additional information is important to obtain from a patient who present with these symptoms?

• Assessment of a patient's alchol intake should always be included in the social history because many people who drink alcohol may not voluntarily admit to having a drinking problem. In addition, we need examination the viral hepatitis serological markers and the liver functional tests.

How is the test 24-urinary copper done?

• The following are directions for collecting a 24-hour urine sample: in the morning scheduled to begin the urine collection, urinate in the toilet and flush away the first urine. Write down the date and time. That is the start date and time for the collection. The patient have to collect all urine that he pass, day and night, for 24 hours. Use the container given to collect the urine. The urine sample must include the last urine that the patient pass 24 hours after starting the collection. Write down the date and time that the last sample is collected. The urine sample may need to be kept cool during the 24-hour collection period. If so, keep the closed container in a pan on ice. Do not put ice in the container with the urine.

What further investigations would confirm the 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 aetiology 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 oestrogens 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. In the series reported by Steindl and colleagues, patients with Wilson's disease had a normal caeruloplasmin and no Kayser- Fleischer (KF) rings.

• Free copper oncentrations can be calculated-though high values (>200 μg/l) suggest Wilson's disease, diagnosis based on such calcula-

tion lacks specificity and is dependent on the accuracy of copper and caeruloplasmin measurement.

• A 24 hour copper estimation is a simple and useful confirmatory test with raised values (>100 μg/24 hours) invariably seen in symptomatic Wilson's disease. 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. Occasionally, despite gross hepatic copper excess, histochemical techniques may fail to demonstrate copper. Determination of hepatic tissue copper concentration by neutron activation analysis or atomic absorption spectrometry may clearly indicate hepatic copper overload. Concentrations greater than 250 μg/g dry weight are accepted as diagnostic of Wilson's disease.

Course. In this patient the liver biopsy revealed a hepatic copper quantification of 763 mcg copper per gram of dry weight (normal is 10-35 mcg/gm).

Due to the presence of Kayser-Fleischer rings, elevated urine copper excretion after penicillamine excretion test, and diagnostic liver biopsy, the patient was diagnosed with Wilson's disease.

What treatment options might you consider and how would you manage this patient?

• 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 penicllamine. Elemental zinc inhibits gastrointestinal copper absorption but its long term effectiveness is unproven. Success of therapy is judged by clinical improvement.

Course. The patient in this case was then treated with penicillamine 250 mg 4 times a day and pyridoxine 25 mg PO daily which improved his urine copper clearance.

However, he developed significant encephalopathy, a progressively worsening coagulopathy with hemolysis and anemia of liver disease, and significant ascites. His liver disease continued to progress over his two week hospital course, and he demonstrated a sub-fulminant course. Liver transplant was unable to be performed due to his history of alcohol use and his poor support network. He was then transferred to a hospital closer to his family.

CASE TWO

Objectives:

1. **Describe when Wilson's disease has to be suspected.**
2. **Recognise the presymptomatic and symptomatic Wilson's disease.**
3. **List the laboratory measurements commonly used to diagnosis the Wilson's disease.**
4. **Describe the patern of hepatic involvement and the histological findings in Wilson's disease.**

A 17 year old woman with no previous medical history presents with a 3 day history of right upper quadrant pain, abdominal distension and bilateral lower extremity edema

– **Past History**: She had fatigue for about 6 weeks along with subjective fevers and occasional headache. The patient no prior history of heart disease, pheripheral vascular disease. She is not taking any medications and has no known drug or food allergies.

– **Family history**: The patient's family history is negative for the presence of liver diseases or neurologic disorders.

– **Physical exams**: right upper quadrant tenderness, slight abdominal distension, and soft abdomen with no hepatospleenomegaly, bilateral lower extremity edema, normal cardiorespiratory exams, and normal neurological exams.

– **Initial laboratory data***: Hb 114 g/l, platelet 155 (decreased), *AST=148 U/l (increased), ALT=83 U/l (increased)*, phosphatase alkaline=73 U/l, total bilirubine =1.6 mg/dl, *albumine=2.5 g/dl (normal 3.5-5.8), protrombine time = 45.5 (normal 11-14 sec), international normalized ratio (INR) = 1.3 (normal 1,0), sodium = 135 mmol/l (normal 133-143).*

– **Instrumental exams**: Chest X-ray – normal, ECG – normal,

– *Abdominal US – moderate ascites, mild diffuse thickness of the gall bladder wall consistent with hepatitis,* otherwise normal.

She was admitted with a provisional diagnosis of **hepatitis**. *Further work up*:

– Ferritin = 231 microgams/l, Iron saturation < 40%

– ANA = neg, AMA = neg, ASMA = neg,

– Hepatitis profile (VHB, HAV, VHC) = neg,

The normal value for liver functional tests you can see in the student's guide Wilson's disease. Basic facts by Adela Turcanu and Elina Berliba, Chisinau 2014, p.51-52

CASE QUESTIONS

1. **When Wilson's disease has to be suspected?**
2. **How to proceed with the work up for Wilson's disease?**
3. **What are the findings in this patient that suggest Wilson disease?**
4. **What is the patern of hepatic involvement in Wilson disease?**

CASE ANSWERS

When Wilson's disease has to be suspected?

• Unexplained liver disease: liver enzyme/test abnormalities (ALT, AST), enlarged liver (hepatomegaly), or features of chronic liver disease, at any age of presentation, unexplained neurologic and/or psychiatric disease, at any age of presentation and family history: first-degree relative diagnosed with Wilson disease.

How to proceed with the work- up for Wilson's disease?

• Always keep a high index of suspicion

• Wilson's disease can be diagnosed in all age groups, but initially you need exclude viral hepatitis (to investigate serological markers for hepatitis B, C, D), autoimmune hepatitis (to investigate autoantibodies), hemhocromatosis (to evaluate the ferritin and seric iron).

• There is no gold standard for diagnosis, which is based on a combination of clinical and laboratory findings

Course: the patient in this case had:

– Ceruloplasmin=13 mg/dL (normal ceruloplasmin=20-45),

– Urine copper = 3200 mcg/l (normal 30 mcg/l),

– Slit lamp exam by ophthalmology revealed Kayser-Fleischer rings.

– Liver Biopsy was done and samples sent for light and electron microscopy. *Light Microscopy*: "Chronic active hepatitis with *early cirrhosis*. A small amount of stainable copper is demonstrated by *Electron Microscopy*: in some of the nuclei. are found accumulations of glycogen particlesparticles. Many mitochondria are of giant size and bizarre shapesand shapes in addition to the membranes of the cristae are widened forming small and large electronforming electronlucent round swellings bordered by a single membrane.

What are the findings in this patient that suggest Wilson disease?

• The key findings are urinary copper levels >100 μg/24h, hepatic copper levels >250 μg/g d.w., ceruloplasmin levels < 20 mg/dL and Kayser-Fleischer rings.

What is the pattern of hepatic involvement in Wilson disease?

• Liver damage is evident early in the natural history. Hepatocytes are ballooned, show multiple nuclei, clumped glycogen, and glycogen vacuolation. Fatty change is usual. Kupffer cells are large, with stained copper tending to be within these, rather than hepatocytes. Mallory's bodies may be seen, simulating acute alcoholic hepatitis. All grades of change from periportal fibrosis, through submassive necrosis, to a coarse macronodular cirrhosis are seen. Cell injury is thought to result from oxidant damage. The wide variation in host response and clinical heterogeneity probably results from genetic and environmental influences on copper protective mechanisms. Knowledge of the specific genetic mutation does not allow precise prediction of subsequent clinical outcome. Patients may be symptomatic or diagnosed after investigation of incidental liver function abnormality.

• The patients with the hepatic form are younger (less than 19 years), whereas patients presenting after the age of 20 frequently have neurological or psychiatric symptoms. The pattern of hepatic presentation of Wilson's disease can be divided into fulminant hepatitis, chronic hepatitis, or cirrhosis. The fulminant type is characterised by progressive jaundice, hypoalbuminaemia, ascites, coagulopathy, encephalopathy, and renal failure. Hepatic necrosis may lead to a sudden flux of copper.

Course: The final diagnosis of this patient was: **Wilson s disease, hepatic manifestations (cirrhosis).**

The patient was treated initially with D penicillamine and is maintained on trientine and her disease has been successfully controlled with medical therapy to date. Latest Liver Biopsy report: moderate steatosis with slight distortion of the hepatic architecture and mild periportal chronic inflammationperiportal inflammation, stage 1 fibrosis.

CASE THREE

Objectives:

1. **Define the prevalence, etiology and pathogenesis of neuro-psychiatric Wilson disease.**
2. **Take an appropriate medical history, including family history suggesting Wilson disease.**
3. **Explain the mechanism of brain alteration in Wilson's disease.**
4. **Describe the psychiatric presentation of Wilson's disease.**
5. **Describe the prognosis and treatment for Wilson's disease on psychiatric presentation.**

A 30-year-old male born of non-consanguineous parents, presented with personality change since the last 8 months. Also he presented the behavioral disturbances in the form of emotional liability, aggressiveness and disinhibition and delusions.

– **Past history**: He had past history of jaundice at 18 years of age which resolved in 3 months.le sister

– **Family history**: He had 2 sisters and 1 brathers. The little sister had unexplained jaundice. His maternal grandmother had a behavioral disturbances many years.

– **Physical examination** at the time of the admission revealed a KF ring obvious on naked eye examination and risus sardonicus. Vitals were normal, and there was no icterus.

– Higher **mental function examination** revealed impaired attention span – 7 days of week forward and 2 days of a week backward, and he was able to comprehend two-stage axial commands. He had impaired abstract thinking and could not explain the meaning of a given proverb.

– **Cranial nerve examination** was normal apart from broken smooth pursuit.

– **Motor system examination** revealed symmetrical rigidity in the limbs. He had tremors of the upper and lower limbs. The tremors were present at rest and increased during action.

– **Laboratory investigations:**

• Complete blood count (CBC) was normal;

• Biochemical analyses: total bilirubin: 0.6 mg%; direct bilirubin: 0.15 mg/dl; total protein: 8.2 g/dl; albumin: 4.8 g/dl; globulin: 3.4 g/dl; serum glutamic oxaloacetic transaminase (SGOT): 35 IU; serum glutamic pyruvic transaminase (SGPT): 22 IU; alkaline phosphatase: 84 U/l, gamma glutamyl transferase: 23 U/l.

• *Serum copper* was 43.3 μg/dl (normal 70–150 μg/dl).

• *The 24-hour urinary copper* was significantly elevated, i.e. 635.52 μg/day (normal 32-64 μg/day).

• *Serum ceruloplasmin levels were decreased*, i.e. <0.08 g/l (normal 0.20–0.60 g/l).

• USG abdomen revealed liver parenchymal disease with minimal free fluid in the abdomen along with splenomegaly. Venous Doppler was normal with no evidence of portal hypertension.

• Magnetic resonance imaging (MRI) brain revealed classical "face of the giant panda"hted images. There were hyperintensities in the caudate, putamen, thalami and pontine tegmentum.

The clinical diagnosis: **Wilson Disease, neuropshiatric manifestation**

CASE QUESTIONS

1. **What neurological symptoms occur in patient with Wilson's disease?**
2. **What is the mechanism for brain alteration in Wilson disease in this patient?**
3. **What signs and symptoms was relevant in this case for established diagnosis Wilson's disease?**
4. **What is the specific treatment of Wilson disease with neuropsihiatric patern?**

CASE ANSWERS

What neurological symptoms occur in patient with Wilson's disease?

• Neurological symptoms occur later, mainly in adolescents and young adults. The most common manifestations include postural and

intentional tremors, dysphagia and contractions of facial muscles, dysarthria, bradykinesia, muscle hypertonia. Psychiatric manifestations may precede neurological signs in the early stages of WD. About 20% of them precede hepatic and neurological dysfunction.

What is the mechanism for brain alteration in Wilson disease in this patient?

• These psychiatric symptoms can be the effects of brain tissues damage caused by copper accumulation, but might be also the concequence of a real comorbidity with affective disorders.

What signs and symptoms was relevant in this case for established diagnosis Wilson's disease?

• The patient was diagnosed as a case of WD on the basis of biochemical abnormalities and presence of Kayser-Fleischer ring. This case illustrates various neuropsychiatric manifestations of WD, how these worsen and become difficult to treat. Our patient had severe neuropsychiatric symptoms as presenting symptoms. He had emotional lability, disinhibition and was severely agitated, restless with delusional thoughts. Presentation of WD with severe psychiatric symptoms is rare. Since the psychiatric symptoms in WD are generally mild, patients may not present with these symptoms.

• A high degree of suspicion and early detection of WD is critical because early initiation of chelation therapy can prevent a catastrophic outcome.

What is the specific treatment of Wilson disease with neuropsihiatric pattern?

• Specific treatment of WD itself can improve psychiatric and behavioral manifestation, although most studies focus purely on neurological changes rather than on psychiatric changes. Treatment with D-penicillamine can lead to neurological exacerbation or the occurrence of neuropsychiatric manifestations, particularly movement disorders, seizures and psychosis. These events may be irreversible and can occur even in previously asymptomatic patients.

• Treatment with Tetrathiomolybdate was associated with excellent results both for neurological symptoms and for psychiatric ones.

Course: For the severe agitation and restlessness, he was given an injection of haloperidol 5 mg IM in BID doses for 2 days. He still

remained agitated and was subsequently given Tab lorazepam 2 mg TID. This was gradually tapered to 1 mg bid over 2 weeks. Haloperidol was replaced with quetiapine 25 mg which was increased to BID over the next 2 weeks. After 2 weeks of inpatient treatment with antipsychotics and sedatives, his behavior was controlled. Trihexyphenidyl 2 mg tid was used to treat tremors and extrapyramidal effects of antipsychotics. Mild increase in rigidity and bradykinesia was noted.

The patient was started on penicillamine 250 mg daily which was gradually increased to 250 mg five times a day supplemented with pyridoxine 40 mg daily. The leukocyte counts were normal at follow-up after 3 months. There was no worsening of neurologic symptoms after the initiation of penicillamine.

CASE FOUR

Objectives:

1. **Discuss the cause of developed diverse clinical manifestations of Wilson' disease.**
2. **Recognize the signs and symptoms of uncommon features of Wilson's disease.**
3. **Describe the mechanisms have been implicated in the pathogenesis of osteomuscular manifestations of Wilson's disease.**
4. **Recognize the renal abnormalities found in Wilson's disease.**
5. **Develop appropriate medical therapy (incliding nutrition recommendations) for patients with Wilson's disease.**

A 20 –year- old man, was admitted with the history of difficulty in walking and painful movements of the limbs for 5 years; these had progressively worsened over the past 3 years.

• **Past history**:

– He was apparently well 5 years earlier, when he developed jaundice which persisted for 4 months. Jaundice was not preceded by anorexia, nausea, vomiting nor was it accompanied by pain in the right hypochondrium, haematemesis, diarrhoea, pruritis or a bleeding tendency. His sensorium had remained normal during the episode of jaundice.

– He recovered from that illness but noticed that he had difficulty in going upstairs coming down stairs and in getting up from the squatting position.

– At the same time, he noticed difficulty in raising his arms up and in holding objects above the head. There had been no distal muscle weakness in the upper or the lower limbs. He could walk with support for the first 6 months of his illness but later, had required crutches. He was bedridden for 6 months prior to admission.

– All movements had been painful from the outset and more so over the past 3 years.

– He also had generalized aches and pains which were aggravated by coughing, sneezing and palpation. He initially responded partially to analgesics but for the past 6 months analgesics had been ineffective.

• **Family history**: There was no history of consanguinity between the parents but one of his maternal cousins had suffered from similar illness and was treated with penicillamine for a short time before he died.

• **Physical exams**: There was no pallor, jaundice, clubbing, cyanosis or peripheral lymphadenopathy. There was no parotid enlargement, palmer erythema, gynaecomastia, testicular atrophy or spider naevi.

Heart rate 90 BPM, respiratory rate 20 BPM, blood pressure 130/90 mm Hg, BMI 24 kg/m^1.

The patient had Kayser Fleisher rings; this was confirmed by slit-lamp examination. He had a sunflower cataract in both eyes. There were no azure lunulae. The skull and the spine were normal.

• A **neurological examination** showed weakness and wasting of muscles acting on the shoulder and hip joints and brisk deep reflexes. The plantar responses were flexor. There were no extrapyramidal signs nor any mental changes. There was no abnormality in the heart, lungs or abdomen.

• **Investigations**

Haemoglobin level, total and differential W.B.C. count, serum cholesterol, creatinine, urea nitrogen, bilirubin, alkaline phosphatase, total proteins, albumin and globulin were all within normal limits. The creatinine clearance was 60% of normal.

Serum calcium levels were 10, 10.8 and 10.3 mg% respectively on three occasions and serum inorganic phosphorus levels were 5.2, 6.0 and 3.0 m% respectively on these three occasions.

Prothrombin time was 18 seconds. Urine showed no abnormality. *The serum copper was 67 and 60/mg. %* respectively on two consecutive days whereas the serum ceruloplasmin was 2.5 and 2.0 mg% respectively on these two consecutive days.

The urinary copper excretion on two occasions was 1060 ug and 120 ug per 24 hours respectively.

The 24 hour urine calcium and phosphorus excretion was 160 mg and 400 mg respectively.

There was evidence of aminoaciduria with excess of alanine and threonine.

The patient refused permission for a liver biopsy. A skeletal survey, during the present admission showed generalised demineralisation without any Milkman's fracture or subperiosteal bone cysts.

A diagnosis of **Wilson's disease presenting with renal tubular acidosis and osteomalacic osteodystrophy** was made.

CASE QUESTIONS

1. **What evidence from patient history and physical examination date suggest Wilson's disease?**
2. **What are the uncommon featurse of Wilson disease?**
3. **What is the sunflower cataract?**
4. **What is the mechanism for musculoscheletal manifestations in Wilson's disease?**
5. **What are the renal abnormalities in Wilson's disease?**
6. **What nutritional recomandations are appropriate in this case?**

CASE ANSWERS

What evidence from patient history and physical examination date suggest Wilson's disease?

He developed unexplained jaundice at 15 years old which persisted for 4 months, his movements had been painful from the outset and more so over the past 3 years, one of his maternal cousins had suffered from similar illness, he had Kayser Fleisher rings; and a sunflower cataract in both eyes. All this signs may suggest the Wilson's disease in this case.

What is the uncommon feature of Wilson's disease?

The uncommon features of Wilson's disease in our patient include a sunflower cataract, osseomuscular and renal manifestations.

What is the sunflower cataract?

• The sunflower cataract has been reported occasionally and is due to deposition of copper in the lens. Similar cataracts are known to occur following the intra-ocular localisation of a foreign body containing copper. When viewed with the naked eye, the appearance was of a greenish disc in the centre of the pupil, and when the pupil kept dilated the disc was said to increase proportionally in size.

What is the mechanism for musculoscheletal manifestations in Wilson's disease?

• Several mechanisms have been implicated in the pathogenesis of osteomuscular manifestations of Wilson's disease. They are: (a) it is a genetic variant of Wilson's disease, (b) it is secondary to renal tubular acidosis, (c) requires prolonged immobilisation on account of disability and finally (d) exhibit hepatic dysfunction.

What are the renal abnormalities in Wilson's disease?

• The renal abnormalities that were present in our patient were aminoaciduria, renal tubular acidosis (type 2) and a reduced creatinine clearance. The latter two could well contribute to the genesis of the osteomuscular syndrome. The most significant biochemical alterations in Wilson's disease are manifested in the metabolism of copper and aminoaciduria. The excessive copper eliminated in the urine, the notable reduction in serum ceruloplasmin, etc., have recently been studied by means of isotopes, and there is still no clear and certain concept as to pathogenesis. Much less verified is the hypothesis which ascribes the initial defect to a deficiency in ceruloplasmin, an inborn metabolic error which gives rise to a defect in the synthesis of this α-globulin—thus promoting a greater absorption of copper by the intestines and subsequent increased excretion of copper in the urine.

What nutritional recomandations are appropriate in this case?

1. The low copper diet is meant to restrict foods that are usually high in copper, especially organ meats, shellfish, dried beans, peas, whole wheat, and chocolate.

2. Drinking water should be analyzed because it may contain too much copper. If the water contains more than 100 micrograms per liter, then bottled demineralized water should be used. This water should contain only 1 microgram of copper per liter. Demineralized water and distilled water are processed differently and may not contain the same amount of copper. Check with the physician or registered dietitian for more information.

3. Avoid drinking alcohol. It can be harmful to the liver, and the liver may already be damaged from Wilson's disease.

4. Read food labels; some prepared foods list the copper content. Always check the labels of vitamin/mineral supplements to see if they contain copper.

5. For better control of copper intake, choose only average portions or serving sizes of foods. Examples of average portions are 3 to 4 oz of meat, fish, or poultry; 1/2 cup of vegetables; one slice of bread.

6. Do not use copper cooking utensils.

Course: The patient in this case was advised to take d-penicillamine 0.5 gm four times a day along. He took d-pencillamine for a period of 5 months and discontinued the same as he failed to obtain symptomatic relief from bone pains and weakness. He was persuaded to restart penicillamine, which he continued for a period of six months. Even at this length of time the patient failed to get relief from his symptoms and therefore discontinued the drug. He failed to attend for follow up thereafter.

CASE FIVE

Objectives:

1. **Describe the "mimic" liver disease in Wilson disease**
2. **Discuss about differencial diagnosis between liver diseases and Wilson diseases**
3. **Describe what genetic testing is currently available for Wilson disease?**
4. **Understand whay in 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 regime.**

A 34-year -old man with a history of hyperlipidemia was admitted to a clinic with symptoms of abdominal pain and mild hematuria. Based on the patient's symptoms, urinary tract infection was initially suspected, but no evidence of renal stone was found. Hyperlipidemia and elevated liver enzymes were shown in the biochemical tests.

– The patient had no history of prior similar illness nor was there a family history of liver disease. The patient's alcohol consumption was around 350 ml of beer 3 times a week.

– Initial laboratory tests revealed the elevated liver enzymes (ALT: 150 IU/L, AST: 45 IU/L, ALP: 466 IU/L, and γ-GTP: 152 Iu/L) and an abnormal lipid profile (T-Cho: 239 mg/dl, TG: 309 mg/dl, and LDL-C: 150 mg/dl), but the markers of viral or autoimmune hepatitis were negative.

– Imagistic exams. Subsequent abdominal ultrasound and CT-scan were indicative of fatty liver.

– Liver biopsy showed diffuse fat deposition (70-80%) in all lobules of hepatocytes with large to medium fat droplets, localized in the portal area. The presence of mild to moderate portal inflammation with the limiting plate intact was also observed in the liver parenchyma. The biopsy assessment was fibrosis stage 1 and activity grade 2Accordingly,

the patient received treatment for NASH in the outpatient clinic, along with advice on making lifestyle changes to improve health.

– However, on subsequent follow-up, NASH remained unresolved, liver enzymes remained elevated (ALT: 106 IU/L; ALP: 413 IU/L; γ-GTP: 105 IU/L) and liver biopsy showed a continuing inflammation in the portal area with the limiting plate partly broken. Interphase hepatitis with bridging fibrosis was observed in some areas with moderate inflammation. Fat deposition had moderately decreased to about 50%, with the presence of small to moderate sized fat droplets.

– The biopsy assessment was fibrosis stage 3 and activity grade 2.

– Further laboratory investigation showed a decrease in the levels of ceruloplasmin (7mg/dl) in sera and the urinary excretion of copper to be 74.2 μg/ in 24 hours, though only traces of copper were detected by liver biopsy.

However, the patient had no apparent neurological sign or symptoms of Wilson's disease.

CASE QUESTIONS

1. **What are the "mimic" liver disease in Wilson's disease?**
2. **How you explain that the Wilson's disease may masqoue steatohepatitis?**
3. **What are the specific considerations when you are suspected autoimmune hepatitis in pediatric and adult patients?**
4. **What genetic testing is currently available for Wilson disease?**
5. **With what medication should the Wilson's disease patient begin treatment?**

CASE ANSWERS

What are the "mimic" liver disease in Wilson's disease?

• The "mimic" liver disease in Wilson's disease are autoimmune hepatitis and steatohepatitis.

How you explain that the Wilson's disease may masqoue steatohepatitis?

• 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 hyperlipide-

mia. 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 regime.

What are the specific considerations when you are suspected autoimmune hepatitis in pediatric and adult patients?

• 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

What genetic testing is currently available for Wilson disease?

• The sequence analysis of ATP7B gene (Wilson disease 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

Course in our patient. Suspicion of Wilson's disease led to diagnostic mutation analysis. Presence of a heterogeneity in the patient's ATP7B gene confirmed Wilson's disease

With what medication should the patient begin treatment?

• There are now new options for the medical treatment of patients with Wilson's disease. Penicillamine is no longer the "treatment of choice," as there is a growing experience with safer and effective alternatives. Trientine may be the best first choice amongst currently approved drugs as initial therapy for symptomatic patients requiring chelation therapy, and may be even more effective when used in combination with zinc treatment. Zinc is an effective medication for maintenance therapy.

Course: Administration of D-penicillamine at a dose of 795 μg/day resulted in an increase in the urinary excretion of copper at 666.7 μg/day. After 10 months of treatment, liver function tests improved (ALT: 48 IU/L; AST: 28 IU/L; ALP: 332IU/L; γ-GTP: 61 IU/L),

and with the help of nutritional counseling, an excess body weight of about 5 kg was lost. Liver biopsy showed overall marked decrease in fat deposition (< 5 %) in the liver, though within the liver parenchyma, bridging fibrosis remained unchanged and fibrotic bands appeared fine but still connected to the portal area.

CASE SIX

Objectives:

1. **Recognise the history and clinical manifestations in Wilson's disease.**
2. **Identify laboratory date used to calculate Nazer prognostic index.**
3. **Understand clinical and laboratory monitoring of patients with Wilson' disease for diagnosis end stage liver disease.**
4. **Describe the complications and prognosis Wilson's disease.**
5. **Describe the indications and contraindications for liver transplantation in Wilson's disease.**

A 21-year-old female was diagnosed with Wilson Disease two weeks before admission in the hospital, on the basis of clinical signs of icterus and hepatomegaly and specific laboratory findings (low serum ceruloplasmin, high urine copper, and no other causes of acute liver failure, such as viral, toxic or autoimmune hepatitis).

- She had no neurological symptoms, no Kayser Fleischer rings
- At the time of the diagnosis of WD she had a moderate form of liver failure, so she was started on treatment with D-penicilamine and zinc, but soon her liver function deteriorated and complicated with renal and respiratory failure.
- Subsequently, she underwent a liver transplantation.
- At the time of transplantation, her MELD (Model for end stage liver disease) score was 26 and the liver profile at the time of liver transplantation revealed increased AST – 649 mg/dL, ALT–310 mg/dL, ALP – 195 mg/dL, total bilirubin – 19.6 mg/dL, direct bilirubin – 13.8 mg/dL, INR – 3.4, prolongation of protrombine time – 20 s, normal serum creatinine – 0.6 mg/dL, low serum albumin – 2.5 mg/dL.
- She was started immediately on immunosuppressive theraphy with daclizumab, followed by tacrolimus and steroids. On the forth day after transplantation she experienced an episode of acute liver rejection, resolved with steroids.

CASE QUESTIONS

1. **Who needs liver transplants in Wilson disease?**
2. **How you determine the Nazer prognostic index?**
3. **What is the prognosis of Wilson Disease?**
4. **Can a carrier (heterozygote) of the Wilson disease gene donate part of his/her liver tissue for a Living Related Donor Transplant to a patient?**

CASE ANSWERS

Who need liver transplants in Wilson disease?

• Our patient was an established case of WD with primary liver involvement, who needed rapid liver transplantation for the management of unresponsive liver failure.

• There are some reports of successful management of acute liver disease by medical therapy. However, if medical therapy fails to suppress the progression of the disease, orthotopic liver transplantation (OLT) is the only alternative treatment. It is indicated for WD patients with acute liver failure when the revised King's score is 11 or higher and patients with decompensated cirrhosis that's unresponsive to chelation therapy. Liver transplantations of these individuals can be achieved by a cadaveric donor or living donor transplant, even if the donor is a heterozygous carrier.

• OLT generally gives excellent results. The one year survival rate and 5 year survival rate in pediatric patients are 90.1% and 89% in comparison with a survival of 88.3% and 86% for adults in a multi-center observational study over 20 years. The OLT also corrects the underlying renal disorder. However, survival is only one aspect of patients' well-being. Neurological complications can be quite common.

• The immunosuppressive agents would leave the patients vulnerable to infections. Lack of compliance in the immunosuppressive agents would lead to acute hepatic failure. Long-term follow-up would be in need to assess the efficacy of OLT.

How you determine the Nazer prognostic index?

• Prognostic scoring systems for WD are a useful tool to direct therapy, identify which patients can be treated medically and which have a high likelihood for death and will require liver transplant. An improvement to the Nazer prognostic index based on serum bilirubin,

INR, and AST. If Nazer scores of 1 to 9, liver function recovers to normal in 6 to 12 months.

What is the prognosis of Wilson Disease?

- In general, if the treatment begins early enough, the outlook is good. If liver failure is only mild to moderate, liver function recovers to normal in 6 to 12 months.
- Unless the liver receives further insult (viral hepatitis, drug damage, etc.), and if the patient complies with therapy, liver function will probably be adequate for a normal life span. Some cirrhosis and portal hypertension may remain and there is a continuing risk of variceal bleeding. This risk lessens over years of anti-copper therapy.
- For patients with neurological symptoms, improvement in symptoms begins about 5 to 6 months after the start of treatment and continues to improve for about 18 months. After 2 years, residual neurological symptoms are likely to be permanent.

Can a carrier (heterozygote) of the Wilson disease gene donate part of his/her liver tissue for a Living Related Donor Transplant to a patient?

- A heterozygote can donate part of his/her liver if it is otherwise healthy, the blood type is compatible, and there are no other medical contraindications. It must also be known with certainty that the donor is just a carrier and does not actually have Wilson disease. This may need to be determined through genetic testing. There are reported cases of heterozygotes donating in this way in the U.S., China, and Japan. Studies show that this option corrects the abnormality of copper metabolism caused by Wilson disease in the recipients.

SELF-ASSESSMENT QUIZ

(for answers for this quiz see the book Wilson Disease. Basic Facts by autors Adela Turcanu and Elina Berliba, Chisinau 2014, page 51)

1. C.M. Among the following, which are the most definitive tests in the diagnosis of Wilson disease?

a) Serum ceruloplasmin.
b) 24-hour urine copper.
c) Serum copper.
d) Hepatic copper.
e) Liver histology.

2. C.M. True statements pertaining to Wilson disease include:

a) Kayser-Fleischer rings are pathognomonic.
b) There is autosomal recessive inheritance.
c) Decreases in serum copper levels cause hemolysis.
d) Heterozygotes have biochemical manifestations of the disease.
e) Symptoms often start in early childhood.

3. C.M. Which of the following should be used in the treatment of most patients with Wilson disease?

a) Penicillamine.
b) Pyridoxine.
c) Triethylenetetramine 2HCI.
d) Phlebotomy.
e) Diet limiting copper-rich foods.

4. C.M. True statements about the neuropsychiatric disorder associated with Wilson disease indude:

a) It usually occurs in a younger age group than the liver disease.
b) Improvement in neurologic symptoms occurs with appropriate therapy.
c) Subtle personality changes may occur.
d) Parkinsonian symptoms are more frequent.
e) Patients are commonly sent to a psychiatrist initially.

5. C.S. What age does Wilson' disease present at?

a) 30-45 years (rarely in childhood).
b) 12-23 years average (rarely over 50).
c) 55-60 years average.
d) 60-70 years average.

6. C.S. Physical exams findings in Wilson's disease is:

a) Alopecia.
b) Sunflower cataract.
c) Dyspnea.
d) Acute abdominal pain.
e) Pruritus.

7. C.S. What happens to serum ceruloplasmine in Wilson's disease?

a) It is increased.
b) It is decresed.
c) It is decresed below 20 mg/dl in 95% of patients.
d) It is increased more than 40 mg/dl in 80% patients.

8. C.S. What is the gene can affect Wilson disease?

a) ATP 7A.
b) ATP 7B.
c) HFE.
d) Defect of Alpha-1 antitrypsin.
e) HLA.

9. C.S. What is most common liver involvement in Wilson disease?

a) Acute hepatitis.
b) Chronic hepatitis.
c) Acute hepatice failure.
d) Hepatocellular cancer.

10. C.S. When are seen the Kayser-Fleischer rings?

a) Kayser-Fleischer rings are seen in at least 98% of patients with neurological Wilson disease.
b) Kayser-Fleischer rings are seen in all patients with hepatic Wilson disease.
c) Kayser-Fleischer rings are seen in at least 85% of patients with hepatic Wilson disease.
d) Kayser-Fleischer rings are seen in all of patients with Wilson disease.

REFERENCES

1. Adela Turcanu, Elina Berliba Wilson's disease. Basic facts. Methodical recomendation. Chisinau, 2014: 52 pp

2. Ala A, Walker AP, Ashkan K, Dooley JS, Schilsky ML: Wilson's disease. Lancet 2007, 369(9559):397-408.

3. Cumings JN. The copper and iron of brain and liver in the normal and in hepatolenticular degeneration. Brain 1948;71:410-415

4. EASL: Clinical Practice guideline: Wilson's disease Journal of Hepatology 2012 vol. 56 j 671–685

5. Dening TR. The neuropsychiatry of Wilson's disease: A review. Int J Psychiatry Med. 1991; 21:135–48.

6. Golding DN, Walshe JM. Arthropathy of Wilson's disease. Study of clinical and radiological features in 32 patients. Annals of the Rheumatic Diseases 1977; 36:99

7. Ferenci P, Caca K, Loudianos G, Mieli-Vergani G, et.al Wilson's disease: the scourge of copper. J Hepatol 1998, 28(4):734-739.

8. Feller ER, Schumacher HR. Osteoarticular changes in Wilson's disease. Arthritis and Rheumatism 1972; 15:259–66.

9. Jackson GH, Meyer A Lippmann S. Wlson's Disease. Psychiatric Manifestations May be the Clinical Manifestation. J Gastroenterol Hepatol 1992; 4:370.

10. Steindl P, Ferenci P, Dienes HP, et al. Wilson's Disease in Patients Presenting with Liver Disease-A Diagnostic Challenge. Gastroenterology 1997; 113:212.

11. Roberts, EA, Schilsky ML. AASLD guideline: A practice guideline on Wilson Disease. Retrieved on August 19, 2006. www. Uptodate.com

12. Huster D: Wilson disease. Best Pract Res Cl Ga 2010, 24(5):531-539.

13. Longe AC, Glew RH, Omene JA: Wilson's disease. Report of a case in a Nigerian. Arch Neurol 1982, 39(2):129-130.

14. Nazer H, Ede RJ, Mowat AP, Williams R. Wilson's disease: clinical presentation and use of prognostic index. Gut 1986; 27:1377–1381.

15. Ormerod JA. Cirrhosis of the liver in a boy, with obscure and fatal nervous symptoms. St Bartholomew' Hosp Rep 1890;26:56-68

16. Roberts EA, Schilsky ML; American Association for Study of Liver Diseases (AASLD). Diagnosis and treatment of Wilson disease: an update. Hepatology. Jun 2008; 47(6):2089-111.

17. Saito T: Presenting symptoms and natural history of Wilson disease. Eur J Pediatr 1987, 146(3):261-265.

18. Scheinberg IH, Sternlieb I. Smith LH. Major Problems in Internal Medicine. Philadelphia: WB Saunders; 1984. Wilson's disease; pp. 86–91.

19. Wilson SAK. Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver. Brain 1912; 34:295-509.

20. Wilson disease mutation database. Available from: http://www.wilsondisease.med.ualberta.ca/database.asp.

21. Wilson DC, Phillips MJ, Cox DW, Roberts EA. Severe hepatic Wilson's disease in preschool-aged children. J Pediatr 2000; 137:719–722.