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Wilson's Disease: An Auto Immune Regenerative Disorder and its Diagnosis by Diagnostic Scoring System

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Abstract

Background: Wilson's disease is an inherited autosomal recessive disorder of copper metabolism. Clinical signs, biochemical parameters, histologic findings and/or ATP7B genetic testing are required to diagnose Wilson's disease.

Case presentation: 25-year-old and 22-year-old young women (siblings) presented to University of Gondar hospital, Northwest Ethiopia, with difficulty of keeping balance of 3 years duration and progressive extremity weakness of 5 years duration respectively. Both siblings had visible ocular Kayser-Fleischer rings, low serum ceruloplasmin level and increased urinary copper content, ultrasound-evidenced cirrhotic liver disease and axial T2- weighted MRI hyperintensities in both basal ganglia and brainstem (mid brain and pons). Diagnosis of Wilson's disease was established in both patients using diagnostic scoring system proposed by '8th International Meeting on Wilson disease and Menkes disease, Leipzig (2001)'. Treatment with D-Penicillamine as chelator and Zinc sulphate as metalothionein-inductor was started. Screening of their family members was recommended.

Conclusion: Wilson's disease, declared to be an orphan disease, requires clinical acumen of physicians and expensive investigation modalities for prompt recognition and inaccessible as required, lifelong drugs for treatment.

Keywords: D-Penicillamine • Zinc sulphate • serum ceruloplasmin • Biochemical parameters

Abbreviations: AST: Aspartate Aminotransferase; ANA: Antinuclear Antibody; BUN: Blood Urea Nitrogen; ESR: Erythrocyte Sedimentation Rate; FLAIR: Fluid-Attenuated Inversion Recovery; HIV: Human Immunodeficiency Virus; HBSAg: Hepatitis B Surface Antigen, MRI: Magnetic Resonance Imaging; RF: Rheumatoid Fac tor; ULN: Upper Limit of Normal; WD: Wilson's Disease.

Introduction

Wilson's Disease (WD) was first described by Kinnear Wilson in 1912, as 'hepatolenticular degeneration'. It is an inherited autosomal recessive disorder, caused by a mutation in the *ATP7B* gene, leading to impaired hepatocellular copper transport and subsequently results in deleterious accumulation of copper in the liver, brain, kidney and cornea. The prevalence of WD is estimated to be 1 in 30,000 individuals in non-consanguineous families [1-5].

The clinical features may vary from asymptomatic state with biochemical abnormalities, acute hepatitis, cirrhotic liver disease, neurologic deficits and psychiatric disorders. Diagnosis is established by clinical scoring system proposed by '8th International Meeting on Wilson disease and Menkes disease, Leipzig (2001)' as presenting clinical and laboratory parameters lack diagnostic accuracy. Symptoms of Wilson's disease can be effectively controlled by medical therapy (chelation therapy, Zinc salts and dietary advice), while liver transplantation is held in reserve for those with severe and advanced liver disease and incapacitating neurologic deficit.

Here, we discourse two cases of Wilson's disease presented with neurologic deficits [6-10].

Case Presentation

This Article is based on review of latest scientific literature presented in journals, books related on energy consumption, Growth and Environment, Internet sources and country data obtained from various ministries of the governments of Ethiopia to collect qualitative and quantitative information.

Based on data collected a comprehensive literature review is carried out on Ethiopia the nexus between Energy Consumption, Growth and Environment in Ethiopian Economy. The article is divided in to five sections: In section 1 introduction, in section 2 methodology parts is discussed.

Section 3 discusses energy prospects of Ethiopia, Theoretical and conceptual considerations. Finally, section 4 summarizes this article with intensive conclusion [11-13].

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Case-1

25-year-old young woman presented to University of Gondar, Northwest Ethiopia, with progressive difficulty of keeping balance of three years duration and change in voice (slurring of speech) and tremor of hands of six months duration. She had no headache, visual disturbance, weakness of extremities, or bladder or bowel problem. She had no memory loss or epileptic fits. Her younger sister has been wheel-chaired due to neurologic problem. No preceding head injury, fever with altered mentation, alcoholism or drug abuse. Serology for HIV infection was negative. No history of yellowish discoloration of eyes, urine color change, or abdominal distension [14-16].

On physical examination, she was nourished, conscious and oriented. His Blood Pressure (BP) was 100/70 mmHg, Pulse Rate (PR) 76 beats per minute, Respiratory Rate (RR) 14 breaths per minute and Temperature (T°) 36.5 °C. His arterial Oxygen Saturation (SaO_2) was 94% with room air. She had pink conjunctivae and non-icteric sclerae. Kayser-Fleischer rings were visible with naked eye. Her lungs, heart and abdomen examinations were unremarkable. On neurologic examination, mini-mental state examination was normal and no cranial nerve abnormalities. No motor or sensory deficits. Tandem walk was poorly performed. She had dysarthria (slurred speech) and intention tremor of hands. Meningeal irritation signs were negative. Presumptive diagnosis of cerebellar disorder due to multiple sclerosis was made. Laboratory investigations including complete blood count, biochemical tests and brain MRI were requested [17-20].

A laboratory examination revealed hemoglobin 15 gm/dl (normal, 12 gm/dl -18 gm/dl), total leukocyte count 5,200/µl (normal, 4000-11,000/µl; granulocyte 54%, lymphocyte 35%), platelet count 87,000/µl (normal, 150,000-450,000/µl) and ESR 1 mm in first hour. Serum biochemical tests were normal. Serum tests for ANA and RF were negative. Serologic test for HIV, hepatitis B and hepatitis C infections were negative. Abdominal ultrasound examination revealed coarse echo-texture liver with surface irregularity. Axial T2- weighted MRI images showed hyperintensities on basal ganglia and brainstem, which was suggestive of Wilson's disease (Figure 1).

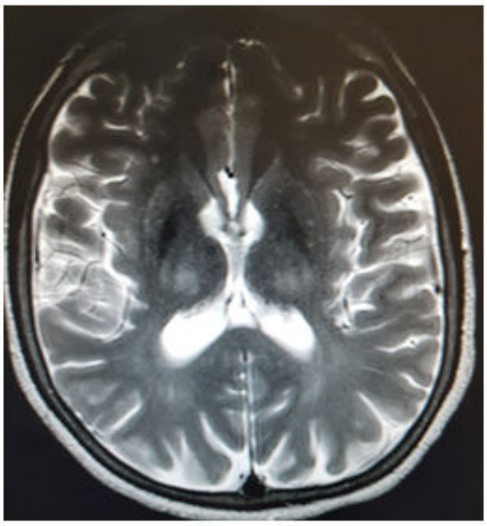

Figure 1. Axial T2-weighted MRI image showing increased signal intensity in basal ganglia (case-1).

Serum ceruloplasmin level by immunoturbidimetry and 24 hr urinary copper content by Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) were determined to support the imaging diagnosis and serum ceruloplasmin concentration was reduced (<10 mg/dl) and 24 hrs urinary copper excretion was increased (142.2 µg/24 hrs). In sum, the clinical signs, biochemical tests and imaging findings met diagnostic criteria for Wilson's disease (K-F rings present, score 2; mild neurologic symptoms, score 1; serum ceruloplasmin level <10mg/dl, score 2; urinary copper content 2xULN, score 2; diagnosis of Wilson's disease established if score ≥4) (Table 1).

Table 1. Laboratory results of case-1 and case-2 at time of clinical evaluation at Neurology Clinic, University of Gondar hospital, Northwest Ethiopia.

Variable	Case-1						Case-2			Ref. value	
Complete blood count	-	-	-	-	-	-	-	-	-	-	-
Hemoglobin (gm/dl)	-	-	15.2	-	-	8.6	-	-	43435	-	-
WBC ($x10^3/µl$)	-	-	5.2	-	-	3.7	-	-	44869	-	-
Platelets ($x10^3/µl$)	-	-	87	-	-	137	-	-	150-450	-	-
ESR (mm/hr)	-	-	-	1	-	-	-	-	-	0-20	-
Liver biochemical tests	-	-	-	-	-	-	-	-	-	-	-
ALT (U/L)	-	-	-	30	-	-	21	-		14732	-
AST (U/L)	-	-	-	41	-	-	40	-	-	14732	-
Alkaline Phosphatase ((U/L)	-	143	-	-	140	-	-	50-250	-	-	-
Bilirubin (total) (mg/dl)	-	0.8	-	-	1.24	-	-	0-3-1.5	-	-	-

Bilirubin (Direct) (mg/dl)	-	0.28	-	-	0.77	-	-	0-0.3	-	-	-
Serum total protein (gm/dl)	-	7.25	-	-	6.2	-	-	44779	-	-	-
Serum Albumin (gm/dl)	-	4.1	-	-	3.6	-	-	3.5-5	-	-	-
Coagulation Profile tests	-	-	-	-	-	-	-	-	-	-	-
Prothrombin time (sec)	-	13.5	-	-	14.6	-	-	41974	-	-	-
Partial thromboplastin time (sec)	29	-	-	34	-	-	25-35	-	-	-	-
INR	-	-	-	-	1.12	-	-	1.24	-	-	0.8-1.4
Renal function tests	-	-	-	-	-	-	-	-	-	-	-
BUN (mg/dl)	-	-	-	26	-	-	12	-	-	15-50	-
Serum Creatinine (mg/dl)	-	1.07	-	-	0.57	-	-	0.6-1.2	-	-	-
Thyroid function tests	-	-	-	-	-	-	-	-	-	-	-
Free T4 (ng/dl)	-	-	1.14	-	-	1.18	-	-	0.8-1.8	-	-
TSH (mIU/ml)	-	-	-	0.86	-	-	0.34	-	-	0.35-5.50	-
Copper studies	-	-	-	-	-	-	-	-	-	-	-
Serum Ceruloplasmin (mg/dl)	-	<10.0	-	-	10.5	-	-	20-60	-	-	-
24-hrs urinary copper (µg/24-hrs)	142.2	-	-	110.5	-	-	3.0-50.0	-	-	-	-
Serum Electrolytes	-	-	-	-	-	-	-	-	-	-	-
Potassium (meq/L)	-	-	3.9	-	-	3.6	-	-	3.5-5.0	-	-
Sodium (meq/L)	-	-	146	-	-	140	-	-	135-145	-	-

Hence, she was started on D-Penicillamine, 300 mg, po, once daily and dose escalated by 300 mg weekly, to reach a target dose of 300 mg, three times daily. She was as well started on Zinc sulphate, 20 mg, po, twice daily, pyridoxine 25 mg, po, daily and advised to avoid copper-rich diet. Then, the patient was scheduled for close follow-up. Screening of family members for Wilson's disease was recommended.

Case-2

22-year-old, wheel-chaired, young woman presented to University of Gondar, Northwest Ethiopia, with progressive weakness of proximal muscles (difficulty to go upstairs and stand from toilet, followed by difficulty of combing hair and at last unable to stand) of 5 years duration and unable to keep balance of 3 years duration. She has been wheel-chaired in the last six months due to neurologic problem [21]. She had transient urinary incontinence. She was treated with high-dose prednisolone (60 mg, po, daily) for six months with no avail. She had no headache, visual disturbance, memory loss or epileptic fits. No preceding head injury, fever with altered mentation, alcoholism or drug abuse. Serology for HIV infection was negative. No history of yellowish discoloration of eyes, urine color change or abdominal distension (Table 2).

Table 2. Diagnostic Scoring System for Wilson's disease Proposed by '8th International Meeting on Wilson disease and Menkes disease, Leipzig (2001).

Kayser-Fleischer rings	No. of Rings	Liver copper (in absence of cholestasis)	No. of Rings
Present	2	>250 µg/g	2
Absent	0	50-250 µg/g	1
		Normal (<50 µg/g)	0
Neurologic symptoms (or typical brain MRI)		Urinary copper (in absence of acute hepatitis)	
Severe	2	Normal	0
Mild	1	1-2× ULN	1
Absent	0	>2×ULN	2
		Normal, but >5x ULN after Penicillamine	2
Serum ceruloplasmin		Mutation analysis	
Normal (>20 mg/dl)	0	Two chromosome mutations	4
10-20 mg/dl	1	One chromosome mutation	1
<10 mg/dl	2	No chromosomes detected	0
Coomb's negative hemolytic anemia			
Present	1		
Absent	0		
Total score	Evaluation		
4 or more	Diagnosis established		
3	Diagnosis possible, more tests needed		
2 or less	Diagnosis very unlikely		

Note: ULN, Upper Limit of Normal.

On physical examination, she was under-nourished, conscious and oriented. His Blood Pressure (BP) was 95/70 mmHg, pulse rate (PR) 80 beats per minute, Respiratory Rate (RR) 14 breaths per minute and Temperature (T°) 36.5 °C. His arterial oxygen saturation (SaO_2) was 94% with room air. She had pallor of conjunctivae and non-icteric sclerae. Kayser-Fleischer rings were visible with naked eye. Her lungs, heart and abdomen examinations were unremarkable. On neurologic examination, mini-mental state examination was normal and no cranial nerve abnormalities. She had proximal muscle weakness and atrophy on both upper and lower extremities. Deep tendon reflexes were variable. Tandem walk was difficult to perform due to weakness. She had head titubation and intention tremor of hands. Finger-to-nose was poorly performed. Meningeal irritation signs were negative. Diagnosis of myopathic weakness and cerebellar disorder due to Wilson's disease was considered after confirmed diagnosis of prior case. Laboratory investigations including complete blood count, biochemical tests, copper studies and Brain MRI were requested.

A laboratory examination revealed hemoglobin 8.6 gm/dl (normal, 12 gm/dl-18 gm/dl), total leukocyte count 3,700/µl (normal, 4000 µl -11,000/µl; granulocyte 57%, lymphocyte 30%) and platelet count 137,000/µl (normal, 150,000 µl-450,000/µl). Serum biochemical tests were normal. Serum tests for ANA and RF were negative. Serologic test for HIV, hepatitis B and hepatitis C infections were negative. Abdominal ultrasound examination revealed coarse echo-texture liver with surface irregularity. Axial T2- weighted MRI images showed hyperintensities on basal ganglia and brainstem, which was suggestive of Wilson's disease. "Face of the giant panda" in the midbrain was spotted on MRI image (Figure 2).

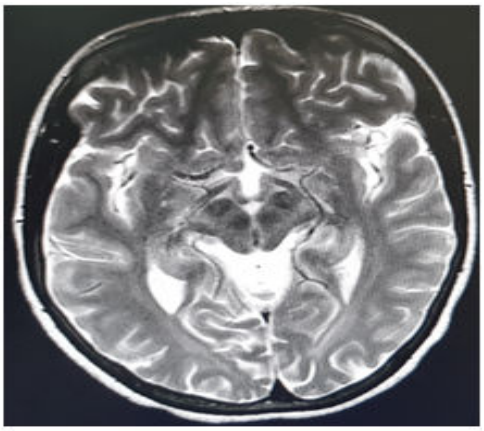

Figure 2. Axial T2-Weighted MRI image Showing Classic 'Face of the Giant Panda' Sign in Mid Brain (Hyperintensity of the Tegmentum Except the Red Nucleus (the eyes), Substantia Nigra (the ears) and Superior Colliculus (the mouth) (Case-2).

Serum ceruloplasmin level was reduced (10.5 mg/dl) and 24-hrs urinary copper content was increased (110.5 µg/24-hrs). In sum, the clinical signs, biochemical tests and imaging findings met diagnostic criteria for Wilson's disease (K-F rings present, score 2; severe neurologic symptoms, score 2; serum ceruloplasmin level =10.5 mg/dl, score 1; urinary copper content >2xULN, score 2; diagnosis of Wilson's disease established with score ≥4). Hence, she was started on D-Penicillamine, 300 mg, po, once daily and dose escalated by 300 mg monthly, to reach a target dose of 300mg, three times daily. She was as well started on Zinc sulphate, 20 mg, po, twice daily, pyridoxine 25 mg, po, daily and advised to avoid copper-rich diet. Then, the patient was scheduled for close follow-up.

Results and Discussion

Wilson's Disease (WD) is an inherited autosomal recessive disorder characterized by impaired hepatocellular copper metabolism. Mutation of ATP7B gene at chromosome 13 encodes defective hepatic copper transporting P-type ATPase at trans-Golgi network and cytoplasmic vesicles, which hinders ceruloplasmin synthesis and biliary excretion of copper. Hence, excess serum 'free' (non-ceruloplasmin bound) copper results in tissue toxicity via oxidative stress and cellular apoptosis in hepatic and extra-hepatic organs (2-4).

Patients with WD present with a variable degree of hepatic (40%-50%), neurologic (50%-60%) and ophthalmologic (50%-90%) manifestations at initial presentation. Hepatic features include asymptomatic state with persistently elevated serum transaminase activity, acute hepatitis, or cirrhotic liver disease. Neurologic features constitute parkinsonism-type with bradykinesia and rigidity; pseudosclerotic-type with tremor, ataxia and dysarthria; and mixed (arrhythmic-hyperkinesia)-type with chorea, athetosis and dystonia. Psychiatric problems appear in WD include inappropriate behaviors, mood changes, depression and acute psychotic features. Kayser-Fleischer rings and sunflower cataracts are ocular indicators of WD. Biochemical findings in WD consist of low serum ceruloplasmin level and increased urinary copper content. Axial T2-weighted MRI images suggest hyperintensities in the basal ganglia, brain stem and cerebellum. "Face of the giant panda" in the midbrain is classic MRI sign (2-10). Diagnosis of Wilson's disease is established by scoring system proposed by "8th International Meeting on Wilson disease and Menkes disease, Leipzig (2001)", which encompasses combination of clinical signs, biochemical parameters, histologic findings and mutation analysis of ATP7B gene. Screening of family members of index case should be routinely practiced to identify and treat early symptomatic and asymptomatic cases.

Conclusion

Our patients presented with symptomatic neurologic deficits, ocular Kayser-Fleischer rings, ultrasound-evidenced cirrhotic liver disease, axial T2-weighted MRI hyperintensities in basal ganglia and brainstem and abnormal copper studies (low ceruloplasmin level and increased urinary copper content). Both patients scored seven using diagnostic scoring system, which established diagnosis of Wilson's disease. D-Penicillamine and Zinc salts were started. Counseling of family members was made.

Medical therapy such as chelators (Penicillamine, Trientine) and Zinc salts effectively control symptoms of WD *via* de-coppering effect and enterocytic metalothionein-inductance respectively. Liver transplantation is indicated in those with fulminant hepatic failure), progressive hepatic dysfunction due to advanced hepatic cirrhosis and severe progressive neurologic deficit unresponsive to chelation therapy. In Conclusion, Wilson's disease, declared to be an orphan disease, requires clinical acumen of physicians and expensive investigation modalities for prompt recognition and inaccessible as required, lifelong drugs for treatment.

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