(International Print/Online Journal)

SJIF IMPACT FACTOR: 4.617
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume3, Issue 1, Page No: 157-160
January-February 2020

Wilson's disease: - A Case Report and Review

Hima Bindu P[1,]*,Gundapaneni Paparayudu[1], D K SaiSruthi[1], S Vinod Naik[1], Dr Varun Lal[2]
[1]Student, [2]Assistant Professor
Department of pharmacy practice, TVM College of pharmacy, Ballari, Karnataka, South India PIN – 583103

***Corresponding Author:**
Dr. Varun Lal
Department of pharmacy practice, TVM College of pharmacy, Ballari, Karnataka, South India PIN – 583103

Type of Publication: Case Report
Conflicts of Interest: Nil

ABSTRACT
Wilson's disease (hepatolenticular degeneration) is a autosomal recessive disorder caused by accumulation of higher levels of Copper (Cu) in tissues/organs, usually liver, brain, eyes, kidneys & bones. Homozygous/compound heterozygous mutation in the ATP7B gene on Ch13q14.3 is a cause of WD. There is defect in ATP7B gene mediated incorporation of Cu into the apoceruloplasmin in WD. Subsequent accumulation of Cu primarily in the liver but and also in brain and other tissues, produce protean clinical manifestation which may include hepatic, psychiatric, neurological, occular and other derangements. Treatment include chelating agents such as D-Penicillamine and Trientine with Zinc sulphate or other zinc salts that leads to reduction of Cu in plasma by reducing zinc absorption and promoting elimination. Here we have discussed etiology, epidemiology, pathogenesis, clinical manifestations, diagnosis, treatment options and also a couple of cases on WD.

Keywords: Wilson disease (WD), Copper (Cu), hepatolenticular degeneration, Ceruloplasmin, ATP7B, chelators, D-Penicillamine, Trientine

INTRODUCTION

Wilson disease (hepatolenticular degeneration) is a autosomal recessive disorder caused by accumulation of higher levels of Cu in tissues/organs, usually liver, brain, eyes, kidneys & skeleton. ATP7B is the only gene responsible for WD. WD is rare but treatable major metabolic disorder.

Aetiology: Homozygous/compound heterozygous mutation in the ATP7B gene on Ch13q14.3 is a cause of WD that encodes a transmembrane Cu P- type ATPase encoded by ATP7B gene.

Epidemiology: Prevalence of WD is varied between 12-29/100000 in European population where as in Asian countries excluding India varies between 33-68/ 100000. Approximately WD affects 1in 30,000 – 40,000 individual. In India there is no community based incidence or prevalence studies.

Normal Cu metabolism: Cu is one of the trace elements whose requirement is about 1-2 mg/day. Dietary Cu is absorbed into the gut and stored within metallothionein in a nontoxic form which is later transported into the systemic circulation by a Cu transporter protein ATP7A on the membrane of enterocytes. Cu is tagged with albumin and transported to the liver where it is uptaken by hepatocytes. ATP7B has six Cu binding units that is responsible for binding of Cu to apoceruloplasmin and forms ceruloplasmin. Ceruloplasmin is either utilized or excreted in bile.

Pathogenesis: In WD, mutation in ATP7B gene results in defective ATP7B protein. Hence Cu eventually starts accumulating within the liver causing liver impairment, the hepatic storage capacity are also exceeds and unbound Cu spills out of the hepatocytes and accumulates in other tissues/organs that causes damage and dysfunction. Cu levels exceed in the blood causing direct toxic effect leading to cellular damage and urinary Cu excretion rises but it is unable to compensate fully for the defect in biliary excretion.

Clinical manifestation:

Hepatic manifestation: In most of the patients with WD liver damage is primary clinical manifestations and onset is more prevalent in age group >10 years. In India and for east countries, the hepatic presentation may occur much early hepatic dysfunction in WD which include asymptomatic enlargement of liver, hepatitis may occur with elevation in blood aspartate aminotransferase (AST), alanine aminotransferase enzymes (ALA), not associated with no elevation or raise in bilirubin levels which spontaneously regress later lead to cirrhosis. Hepatic decompensation, hepatic encephalopathy are complications associated with this condition.

Neurologic manifestation: Usually neurological manifestation of WD occur in patients in early twenties. Magnetic resonance imaging and computed tomography and CT reveals damage mainly in the basal ganglia and other parts of brain and cause neurological problems like dystonia, incoordination and tremor. Dysarthria and dysphagia are also the common symptoms. The symptoms sometimes closely resemble Parkinson's disease. Autonomic disturbance such as orthostatic hypotension, bowel, bladder and sexual dysfunctions etc., can occur. Seizures, headache is infrequent.

Psychiatric manifestation: They may occur at some time in many of the patients. Neurological dysfunction that includes mood disturbances, particularly depression, personality changes, cognitive impairment.

Ophthalmic manifestation: Kayser-Heisher ring is a common opthalmological sign and the easiest ways to identify WD. Eye tissue are transparent which helps in observe the deposition of Cu in tissue. Deposition of Cu is found in descemet's membrane and on the surface of endothelial cells. Patients with Kayser-Heisher rings have high levels of 24hrs urinary Cu and lower levels of ALA.

Other manifestation: Patients with WD are more prone to osteoporosis and fractures due to low bone mineral density. Osteoporosis and osteomalacia is one of the manifestations in WD. Tubular dysfunction with consequent hypercalciuria and hyperphosphaturia may cause calcinosis. Hyperkalemia, muscle weakness and respiratory failure were observed.

Gynaecological abnormalities(irregular menstruation, delayed puberty), cardiovascular dysfunction and other impairment include glucose intolerance, parathyroid insufficiency. Hemolytic anemia may occur due to oxidative damage of erythrocyte by copper. Thrombocytopenia may also develop.

Diagnosis: Serum ceruloplasmin is reduced to < 20mg/ml in WD patient. Normal serum ceruloplasmin is 19-40 mg/dL. Urinary Cu excretion is found to be elevated in WD i.e., >100mcg/day. Normal urinary Cu excretion is <40mcg/day (0.6 mcg mol/day). Liver Cu content and liver biopsy – Cu content is elevated i.e., >200mcg/g dry weight in WD. Normal liver Cu content is <50mcg/g dry weight. KF ring by slit lamp examination. In patient with KF ring, a serum ceruloplasmin level < 0mcg/dL and per day urinary Cu excretion >40mcg/day establish the diagnosis of WD.

Serum Cu and serum free Cu (which is not bound to ceruloplasmin), serum Cu is difficult to get laboratories, and moreover it can also be calculated by indirect method. Normal range is 10-15mcg/dL. Radiolabeled Cu testing- directly hepatic Cu metabolism assays.ATP7B mutation analysis by Genetic testing. Brain imaging, abdominal imaging, LFT, RFT etc are also important in WD.

Treatment: Non-pharmacological therapy: Patients with WD must reduce the consumption of foods rich in copper cocoa powder, chocolate, liver, nuts, mushrooms sunflower seeds and shellfish.

Pharmacological therapy: This therapy concentrates on promoting Cu elimination and reducing Cu absorption.

Dimercaptol: It is the first drug to be introduced in India to treat WD. There was no any significant improvement with this drug. Moreover after introducing Penicillamine, BAL was not in use.

D-Penicillamine: Remains the standard treatment. D-Penicillamine chelates Cu and favours its urinary Cu excretion. Initial 75mg – 1.5g/day orally results in an initial 24hrs cupriuresis of over 2mg/day. Maintenance up to 2g/day, based plasma Cu level. Absorption is 50% if it is taken with a meal hence it is advised to take 1-2 hours after food. To increase tolerance giving lower dose initially 125-250mg/day and gradually increasing over a few weeks is required. In spite it's benefits in WD, it has serious

Volume 3, Issue 1; January-February 2020; Page No.157-160

adverse effects whose use remains controversial for decades. Neurological worsening, fever, rash, lymphadenopathy and late reactions such as bone marrow and renal toxicity etc. There is depletion of pyridoxine level hence supplementation is necessary 20-50mg/day.

Trientine: it is a Cu chelator who's mechanism of action resembles penicillamine. Adult dose is 750-1250mg/day orally in 2-4 divided dose, may be increased to maximum of 2g/day. Pediatric dose is 500-750mg/day orally in 2-4 divided doses for children age 12years and under, may be increased to maximum of 1500mg/day. Trientine is less potent and has less side effects when compared to Although the side effects are less frequent and D-Penicillamine. Adverse effect include dyspepsia, anemia caused by iron deficiency, muscle cramps and spasm, and dystonia. Lupus nephritis and sideroblastic anemia have also been reported with Trientine.

Zinc: administration of zinc reduces intestinal absorption of Cu. The dosing of zinc is 150mg of elemental zinc in 3 divided doses and paediatric dose is 75mg/day in 3 divided doses. It is successfully being used as first line therapy. Both the AASLD and EASL guidelines recommend including a chelating agent in the initial treatment of symptomatic patient (D-Penicillamine/trientine) although trientine may be better tolerated. Zinc is generally well tolerated.

Ammonium tetrathiomolybdate: It has two different mechanisms which reduces intestinal Cu absorptionby forming non-absorbable complex and forms the same complex within the blood stream, preventing cellular Cu uptake. It require complicated dosing scheme because of dual capability therefore a 20mg dose is given 6 times per day, 3times daily with meal and 3 times daily between meals. It is not recommended for long term treatment by only for an initial 8week period, which is to be followed by long term maintenance therapy with zinc. This drug is well tolerated, although bone marrow depression, with anemia or leukopenia may occur.

Surgery: Surgery mainly involves spleenectomy and orthotopic liver transplantation (OLT). Orthotopic liver transplantion is suitable for decompensated liver disease or refractory disease that can not be alleviated by medicational one and it is the only viable option for patients with WD and fulminant liver disease (FHF)/abdominal problems. OLT is highly costly. Hemodialysis- it can reduce the level of Cuin patients with WD in a short period of time. Symptomatic treatment- Despite the general treatment with chelation therapy and zinc is well, additional treatment to control the disturbing symptoms. Neurological symptoms are more refractory than hepatic damage.

CASE REPORT

Patient 1: A 30years old male patient was presenting complaint of generalised weakness since 3 days and passing black coloured stools since 3 days. Patient is known case of WD since 15years and known case of chronic liver disease with portal hypertension since 10years.Patient had hepatic encephalopathy and was treated one year back. Patient is now diagnosed as WD with decompensated liver disease with portal hypertension. Patient was on regular medication ie,. Syrup Zinc gluconate, Tab.Penicillamine, Tab.Propranolol, Tab.Ursodeoxycolic acid.

Investigation: Liver biopsy report shows accumulation of Cu in hepatocytes 258 mcg/g. Liver enzymes such as aspartate aminotransferase are elevated. Prothrombine time is increased to 19sec.

Treatment: Patient was treated with Inj. Pantoprazole 40mg o.d., Inj. Vitamin K 10mg o.d., Tab. Iron pyrophosphate liposome 40mg, Syrup Zinc gluconate 7.5ml t.i.d., Tab. Penicillamine 250mg b.i.d., Tab. Propranolol 20mg o.d., Tab. Furosemide+ spironolactone 20/50mg b.i.d.,

Discussion: Penicillamine maximum dose is 2g/day but is receiving500mg/day dose must be increased to reduce the hepatic damage and prevent neurological manifestation. This drug can cause depletion in pyridoxine level hence supplementation must be provided. Patient is given iron tablet and zinc syrup co-administration decreased absorption of either elements hence patient is advised to give at least 2 hours gap between these 2 medication.

Patient 2 A 23 old female patient was presented with complaint of seizures for first time multiple episodes associated with uprolling of eyes (generalized tonic clonic seizures). Patient is known case of WD since 10years and is on Tab. Zinc sulphate) and Tab. Penecillamine (irregular medication). On examination vitals- BP and PR are elevated. Systemic examination- CNS drowsy and non-oriented other

Volume 3, Issue 1; January-February 2020; Page No.157-160

review of systems are normal. Patient was diagnosed as Wilson's disease with seizures.

Investigations: KF ring was positive. Urinary Cu level is 179mcg/day. Liver function test and renal function test were normal. Tone and power was increased on right side. Reflex plantar.

Treatment: patient is treated with Inj. Phenytoin given initially 800mg followed by 100mg t.i.d., Inj. Lorazepam 4mg o.d., Inj. Levetiracetam 500mg b.i.d., Tab. Zinc sulphate 440mg b.i.d.

Discussion: Medication non adherence is a serious problem especially in chronic disease which may cause worsening of disease, complications, therapeutic failure, frequent hospitalization and increase in health cost of patient.

STATEMENT OF HUMAN AND ANIMAL RIGHTS: All procedures performed in human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

INFORMED CONSENT Written informed consent was obtained from patient 1 and patient 2 for anonymized patient information to be published in this article.

ACKNOWLEDGEMENT: We want to thank our Principal Prof. Dr. Manjunath V Jali and HOD of Pharmacy Practice Prof. Dr. H. N Girish for their guidance and support.

REFERENCE:

1. Castro K I R, Urrutia FJ H, Sturniolo G C. Wilson's disease: A review of what we have learned.*World Journal of Hepatology*December 2015;Vol- 7(29).
2. Pfeiffer R F. Wilson's disease.*Reprinted with permission for Thieme MedicalPublishers* 2007; Vol-27(2):123-132.
3. Dong Q U, Zhi- Ying Wu. Advance in the pathogenesis and treatment of Wilson disease. *Translational neurodegeneration* 2012; Vol-1(23).
4. TalyA B, Prashanth L P, Sinha s. Wilson's disease: An Indian perspective.*NeurologyIndia* sep-oct 2009 vol-57(5).
5. Liu J, Luan J, Zhou X, Cui Y and et al.Epidemology, diagnosis and treatment of Wilson's disease. *Intractable and Rare Disease Research* 2017; Vol-6(4):249-255.
6. Socha P, Janczyk W, Dhawan A, Baumann U and et al, Wilson's Disease in Children: A Position Paper by the HepatologyCommitte of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. *Journal of Pediatric and Gastroenterology and Nutrition*February 2018; volume-66(2).
7. Hermann W.Classification and differential diagnosis of Wilson's disease.*Annals of Translational Medicine*2019;Vol-7(2):S63.
8. Prashanth L K, Taly A B, Sinha S, Arunodaya G R, Swamy H S. Wilson's disease: diagnostic errors and clinical implications*JNeurolNeurosurg Psychiatry* 2004; Vol-75:907–909.
9. Gow P J, Smallwood R A, Angus P W, Smith A L.Diagnosis of Wilson's disease: an experience over three decades.*Gut* 2000;46:415–419.
10. Hajare Q, Mehdi K.Kayser-fleisher ring in Wilson's disease.*Pan African Medical Journal* 2018;30:137.
11. Chang I J, Hahn S H.The genetics of Wilson disease *Hand Clin Neurol*. 2017; 142: 19–34.
12. Shah H, Vankar G K Wilson's Disease : A Case Report*Indian Journal of Psychiatry* 2003; Vol-45 (IV) 253-254.
13. Kasper, Dennis L.,, et al. Harrison's Principles of Internal Medicene. 16th edition. New York:McGraw Hill Education, 2015.
14. Nagral A, Sarma M S, Mathai J, Kukkle P L et al. Wilson's Disease: Clinical Practice Guidelines of the India National Association for Study of the Liver, the India Society of Pediatric Gastroenterology, Hepatology and Nutrition, and the Movement Disorders Society of India.
15. Roberts E A, Schilsky M L. Diagnosis and treatment of Wilson Disease: An update AASLD practice guidelines.*Hepatology Journal* June 2008.
16. Czlonkowska A, LitwinT.Wilson disease – currently used antiCopper therapy. *Handbook of Clinical Neurology*, Vol. 142 (3).
17. Purchase R the treatment of Wilson's disease, a rare genetic disorder of Copper metabolism. *Science Progress* 2013; Vol-96(1), 19–32.
18. Lie W J, Chen1 C, You1 Z F, Yang R M. Current Drug Managements of Wilson's disease: From West to East.*Current Neuropharmacology* 2016; Vol-14, 322-325.

Volume 3, Issue 1; January-February 2020; Page No.157-160