IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Case Report
June 2019 Vol.:15, Issue:3

Wilson's Disease- A Rare Case Report

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

K. SAI VASUDEV*[1], T. AVINASH[2]

[1,2] VI/VI Pharm D, Chebrolu Hanumaiah Institiute of Pharmaceutical Sciences, Guntur,522503, A.P, India.

Submission: 26 May 2019
Accepted: 31 May 2019
Published: 30 June 2019

www.ijppr.humanjournals.com

Keywords: Wilson's disease, ATP-7B, Autosomal, Copper, Neurological, Hepatic.

ABSTRACT

It is an autosomal recessive inherited rare disorder where we observe a defective metabolism of the copper. The patients suffering from the disease typically presents with neurological, psychiatric, hepatic complaints. Its incidence worldwide is 1 case per 30,000-50,000 individuals. The prevalence of this disease is approximately 30 individuals per million population and its rate increases in consanguineous populations. Wilson's disease is a familial syndrome; the risk of the disease in relatives of the index case is 25% for siblings and 0.5% for parents and children. The disease typically manifests in the patient age group of 5-35 years. Patients suffering from this disease have hepatic complaints that are seen in the first decade of life followed by neuropsychiatric events in the second and third decades. This disorder is due to the defective function of the P-type ATPase encoded by ATP-7B gene located on 13q14 which is having 21 exons. This gene is responsible for the balancing of the copper levels in the body by excretion of excessive levels of copper into bile or the blood. Pharmacological management includes chelation therapy, supportive measures for the associated neuropsychiatric and other manifestations. Untreated disease leads to fulminant liver failure and death.

INTRODUCTION:

Wilson's disease is commonly abbreviated as WD. It is an autosomal recessive inherited disorder where we observe a defective metabolism of the copper. The patients suffering from the disease typically presents with neurologic, psychiatric, hepatic complaints. This disease is termed as rare disease by the National Institute of Health (NIH). Its incidence worldwide is 1 case per 30,000-50,000 individuals. The prevalence of this disease is approximately 30 individuals per million population and its rate increases in consanguineous populations[(1)]. Wilson's disease is a familial syndrome; the risk of the disease in relatives of the index case is 25% for siblings and 0.5% for parents and children. The disease typically manifests in the patient age group of 5-35 years but is also associated in children under 2 years and elderly in their early 70 years. The disease has male preponderance.

The disease was for the first time described by Kinnier Wilson who was an English neurologist during the early 20 th century, during the same period Kayser and Fleischer identified the characteristic relation of the pigmentation of the cornea with the underlying neurological and hepatic abnormalities. Half of the patients suffering with the disease presents with hepatic manifestations and the other half with neurological manifestations. The patients experiencing neurological complaints may or may not have the associated hepatic complaints and a small portion of the patients may have complaints relating to blood disorders and behavioral disorders. Patients suffering from this disease have hepatic complaints that are seen in the first decade of life followed by neuropsychiatric events in the second and third decades. Approximately 80% of the intestinal copper is absorbed and is transferred to the liver after reaching the liver the copper is incorporated into the copper binding enzymes, proteins like Ceruloplasmin. In normal individuals excessive amounts of copper is made nontoxic by forming complexes with apo-metallothionein forming copper metallothionein or excreted by hepatobiliary excretion. In patients suffering from this disease copper incorporation or the biliary excretion are defective. This disorder is due to the defective function of the P-type ATPase encoded by ATP-7B gene located on 13q14 which is having 21 exons. This gene is responsible for the balancing of the copper levels in the body by excretion of excessive levels of copper into bile or the blood. Mutations in this gene cause this disease. Decreased or absent ATP7B protein function due to the mutations leads to decreased biliary secretion, decreased ability to incorporate copper into ceruloplasmin[(2)]. This excess copper leads to free radical formation and this causes lipid and protein oxidation

eventually leading to hepatocellular injury, as the copper level increases in the liver it is released into the blood circulation and thus reaches other organs. Hepatic manifestations include hepatomegaly, steatosis progressing to fibrosis and cirrhosis. Brain deposition leads to increased pigmentation, degeneration of basal ganglia, cortical white matter and central pontinemyelenosis. Neurological symptoms are seen mostly in the second decade and the symptoms include rigidity, seizures and tremor, the tremor is seen in the upper limbs is asymmetric and bilateral. Parkinsonism with dystonia, bradykinesia, dysphagia, dysathria is observed [(3)]. Nearly about half of the patients having neurological symptoms also have psychiatric features like depression and overt psychosis. Ophthalmologic manifestation like the presence of Kayser Fleisher rings are seen in about 80-85% of the patients with the hepatic manifestations and nearly all the patients with the neurological presentations. These rings occur due to accumulation of the copper in the descemets membrane around the cornea of the eye. This disease can be of the following 4 stages:

Stage- I: This is the initial period where the copper accumulates in the hepatic binding sites.

Stage- II: Acute copper redistribution in the liver, associated with its release into the circulation.

Stage- III: The chronic deposition of the copper in the extrahepatic tissues and brain leading to fatal disease which is gradually progressive in nature.

Stage- IV: With the effective chronic chelation therapy, normalization of the copper balance.

The diagnosis can be established by the presence of increased hepatic copper concentration, presence of KF rings by the slit lamp examination, elevated 24-hour urinary excretion of the copper levels, low serum ceruloplasmin and the presence of neuropsychiatric symptoms but the liver biopsy is the gold standard diagnosis. Pharmacological management includes chelation therapy, supportive measures for the associated neuropsychiatric and other manifestations. Untreated disease leads to fulminant liver failure and death. We present a case of Wilson's disease[(4)].

CASE REPORT

A 22 years old female patient was presented with the complaints of unsteadiness of gait, inability to speak, 4 episodes of movements of right upper, lower limbs and mouth since 2

days. There is no loss of consciousness or drooling of saliva or incontinence. The attenders of the patient reported that she had complaints of tremors of both lower limbs, behavioral abnormalities, difficulty in speaking 4 months ago. The patient is a known case of Wilsons disease diagnosed 1 year back and is using Zinc, Penicillamine irregularly for the disease. The patient's brother is also known to have Wilson's disease and this patient is the product of consanguinity. The patient also complaints of irregular menstrual cycles and is having a cycle once in two months. On examination patient was anarthric. The vitals of the patient were stable. There were no abnormal laboratory investigations. CT scan of the brain revealed the presence of white matter hypodensities in the bilateral frontal and right parietal lobes, atrophy of the midbrain, superior cerebellar peduncles and pons with the dilation of the ventricle associated with the volume loss of the bilateral lentiform nucleus and diffuse cerebral volume loss. KF rings were observed in the slit lamp examination. Based on these symptoms and investigations she was diagnosed with Wilson's disease and was prescribed with the following medications.

Inj Levetiracetam 1gm in 100 ml NS IV BD, from hospital day 1- 7 and continued as 500 mg tablet BD as discharge medication.

Tab Clobazam 10 mg PO HS from hospital day 1 and continued as discharge medication.

Tab Trihexyphenidyl 2 mg PO BD from hospital day 1-7

Tab Levodopa+Carbidopa 100+10 mg ½ tab PO TID from hospital day 1- 6

Tab Elemental Zinc 167 mg PO TID from hospital day 1 and continued as discharge medication.

Tab Clonazepam 0.25 mg PO HS from hospital day 1-7

Tab Lorazepam 1 mg PO TID from hospital day 7 as discharge medication. On the first 2 days the patients seizures were poorly controlled, and on all the hospital days the patient was anarthric, and the features of dystonia and parkinsonism were present and they gradually improved on the day 7 and the patient was discharged on day 7 with the advice of avoiding the copper rich diet like liver, shellfish and the patient was advised regarding the expected side effects of the drugs.

DISCUSSION

The risk factors for the Wilsons disease in this patient were consanguinity and her brother being a known case of the disease. The patient developed the disease at the age of her 21 years justifying the occurrence of the disease was seen mostly in the age group of 5-35 years. This disease is most commonly seen in males but effects females too. Generally, 25% of the patients who had the disease will have their siblings already affected[5]. Mostly during the first decade of the disease, hepatic manifestations will be evident but in this patient there were no hepatic manifestations and the patient is having neurological manifestations like seizures, anarthria, dystonia, parkinsonian features without hepatic involvement as of now. Wilson's disease also effects the functioning of gonads. In this patient it was evident that the patient had irregular menstrual cycles, and gradually the use of zinc rectifies the function of gonads, but as the patient was not taking her medications regularly she is continuing with her menstrual problems. The past medical history of the patient like tremors and behavioral abnormalities are also suggestive of the neurological illness of the Wilsons disease. Tremor is the most initial neurological symptom which occurs in half of the patients, and our patient experienced this 4 months before her present presentation. The tremor seen in the patients affected with the disease are typically asymmetric, resting or postural. Frequent early symptoms of the disease may include difficulty in speaking, increased salivation, ataxia, masklike facies, clumsiness with the hands, and personality changes. Our patient had experienced personality, behavioral problems, and difficulty in speaking 4 months back as a part of her early symptoms[6]. Late neurological manifestations of the disease include seizures, rigidity, dystonia and flexion. Our patient experienced seizures, dystonia, and rigidity as her late manifestations. Generally, in most of the patients late manifestations rarely occur due the earlier diagnosis and treatment. In our patient these late manifestations can be attributed to the irregular use of the chelation therapy, progressing the neurological illness of the patient. KF rings are seen in about 95-98% of the patients having neurological disease who have not received the chelation therapy. In our patients the presence of KF rings can be attributed to the irregular use of the chelation therapy. The neurological features of WD are chiefly due to the deposition of copper in the lenticular nuclei, although areas like the brainstem and cerebellum can be affected. In our patient these neurological symptoms were due to volume loss of the bilateral lentiform nucleus, atrophy of the midbrain, superior cerebellar peduncles, pons with white matter hypodensities in bilateral frontal and right parietal lobes due to the accumulation of copper. The neurological symptoms are usually

secondary to the cerebral copper deposition, which is sufficient to destroy the nerve cells. Focal seizures occur in about 6% of the patients. Our patient also developed focal seizures due to poor disease control because of irregular therapy. Hypodensity in the bilateral frontal lobe and atrophy of the cerebellum led to gait abnormality in this patient as the frontal lobe is responsible for the voluntary movements and cerebellum is responsible for regulating the motor activities. The occurrence of dystonia can be linked to the volume loss of the bilateral lentiform nucleus which controls the involuntary and unnecessary movements[7].

Initially, symptomatic patients, patients with active disease should be managed with chelating drugs. The combination of zinc and chelating agents is more effective than chelators alone in active disease. In this patient during her initial diagnosis 1 year back, was prescribed with both chelating agents and zinc. Now the chelating agent Penicillamine was discontinued and was continued with zinc. The 24-hour urinary copper level should range from 200 to 500 mcg per day in the patients on chelation therapy. The indicators of an effective response to zinc treatment include 24-hour urinary copper levels less than 75 mcg[8]. Transition to Zinc monotherapy takes place with ion 1-5 years of successful chelator therapy. Penicillamine therapy is known to exacerbate neurological illness in about 50% of the patients during the initial use of the drug. The patient was prescribed with the Levetiracetam to control the seizure activity. Tab Clobazam was prescribed as add on therapy for seizures along with Levetiracetam and to improve the sleep. Tab Trihexyphenidyl, Levodopa+carbidopa was prescribed to manage the dystonia and parkinsonian features, Tab Lorazepam was prescribed to prevent the seizures. Elemental zinc was continued as a maintenance therapy for Wilson's disease[9].

CONCLUSION

This case report delivers the highlights needed to familiarize the physicians about this rare, life threating, uncommon entity.

ABBREVIATIONS

CT: Computerized Tomography

NIH: National Institutes of health

WD: Wilsons Disease

CONSENT

Written informed consent was obtained from the patient for publication of this case.

Funding: No funding sources

ACKNOWLEDGEMENT

I am thankful to my professors, lecturers of Chebrolu Hanumaiah Institute of Pharmaceutical Sciences.

CONFLICT OF INTEREST

There is no conflict of interest.

REFERENCES

1. AyseKacarBayram et.al, Neurological features and management of Wilson disease in children: an evaluation of 12 cases, Turk Pediatri Ars. 2016 Mar; 51(1): 15–21.
2. Annu Aggarwal, and Mohit Bhatt, Advances in Treatment of Wilson Disease, Tremor Other HyperkinetMov (N Y). 2018; 8: 525.
3. Kryssia Isabel Rodriguez-Castro, Francisco Javier Hevia-Urrutia, and Giacomo Carlo Sturniolo, Wilson's disease: A review of what we have learned, World J Hepatol. 2015 Dec 18; 7(29): 2859–2870.
4. Prof Oliver Bandmann et.al, Wilson's disease and other neurological copper disorders, The Lancet, Neurology, Volume 14, Issue 1, P103-113, January 01, 2015.
5. Peter Hedera, Update on the clinical management of Wilson's disease, ApplClin Genet. 2017; 10: 9–19.
6. Mani Kant Kumar, Vijay Kumar, and Praphul Kumar Singh, Wilson's Disease with Neurological Presentation, without Hepatic Involvement in Two Siblings, J ClinDiagn Res. 2013 Jul; 7(7): 1476–1478.
7. AlexandreAluizio Costa Machado et.al, Neurological manifestations and ATP7B mutations in Wilson's disease, Parkinsonism and related disorders, April 2008Volume 14, Issue 3, Pages 246–249.
8. Tomasz Litwin et.al, Neurological manifestations in Wilson's disease –possible treatment options for symptoms, Expert Opinion on Orphan Drugs, Volume 4, 2016 - Issue 7, Pages 719-728.
9. L K Prashanth et.al, Wilson's disease: diagnostic errors and clinical implications, J Neurol Neurosurg Psychiatry. 2004;75: 907–909.