Nepal Journal of Neuroscience 8:155-157, 2011

Late Onset Wilson Disease with Neurologic Involvement Without Kayser-Fleisher Ring

Shree Ram Sharma, MD, DM
Department of Neurology
North Eastern Indira Gandhi Regional Institute of Medical Sciences
Shillong, India

Nalini Sharma, MD
Department of Neurology
North Eastern Indira Gandhi Regional Institute of Medical Sciences
Shillong, India

K.G. Lynrah, MD
Department of Neurology
North Eastern Indira Gandhi Regional Institute of Medical Sciences
Shillong, India

Lyngdoh Monaliza, MD
Department of Neurology
North Eastern Indira Gandhi Regional Institute of Medical Sciences
Shillong, India

Address for correspondence:
S.R. Sharma, MD, DM
Department of Neurology
North Eastern Indira Gandhi Regional Institute of Medical Sciences
Shillong, India
E-mail: srmsims_sharma@rediffmail.com

Received, 22 September, 2011
Accepted, 20 October, 2011

Wilson's disease, also known as hepato-lenticular degeneration, is a rare familial disorder inherited as an autosomal recessive trait with inborn error of copper metabolism leading to toxic accumulation of copper in the body particularly the liver, brain, cornea and kidney. It is a rare event for Wilson disease to have onset in old age with neurological symptoms. And it is rarer for such a condition to occur in the absence of Kayser-Fleischer ring.We report a case of 66 year male who presented with neurological symptoms of Wilson disease without Kayser-Fleischer ring which was confirmed by raised urine copper levels and Magnetic resonance imaging (MRI) features of Wilson disease.

Key words: kayser-Fleischer ring, magnetic resonance imaging, neurological manifestation, Wilson Disease

Wilson's disease, also known as hepatolenticular degeneration was first described by Kinnear Wilson in 1912.[13] It is a rare familial disorder inherited as an autosomal recessive trait with inborn error of copper metabolism leading to toxic accumulation of copper in the body particularly the liver, brain, cornea and kidney.[4] It is characterized by a reduction in the synthesis of the copper transporter protein ceruloplasmin. The patients usually present first time as adolescents or young adults. The onset of the disease in the old age is rare. Overall, it is rare for the disease to have its onset in the old age and have neurological symptoms as the initial symptoms and it is even rarer to see such a patient without eye involvement. We report one such case of Wilson disease with late onset neurological disease without Kayser-Fleischer Ring.

Case Report

A 66 years male presented with complaints of swaying to right side while walking since 6 months. The symptom did not worsen during night. There was no history of difficulty while walking through narrow and dark corridors. He had difficulty in writing and holding objects due to intentional tremors in the right hand. He had no history of truncal ataxia, diplopia or slurring of speech. No history suggestive of cranial nerve involvement, motor or sensory deficits, meningeal involvement. Patient is a known type 2 Diabetic on regular treatment. He was diagnosed to have chronic liver disease with portal hypertension 5 months back and had undergone sclerotherapy and banding for variceal bleed. His family and personal history was

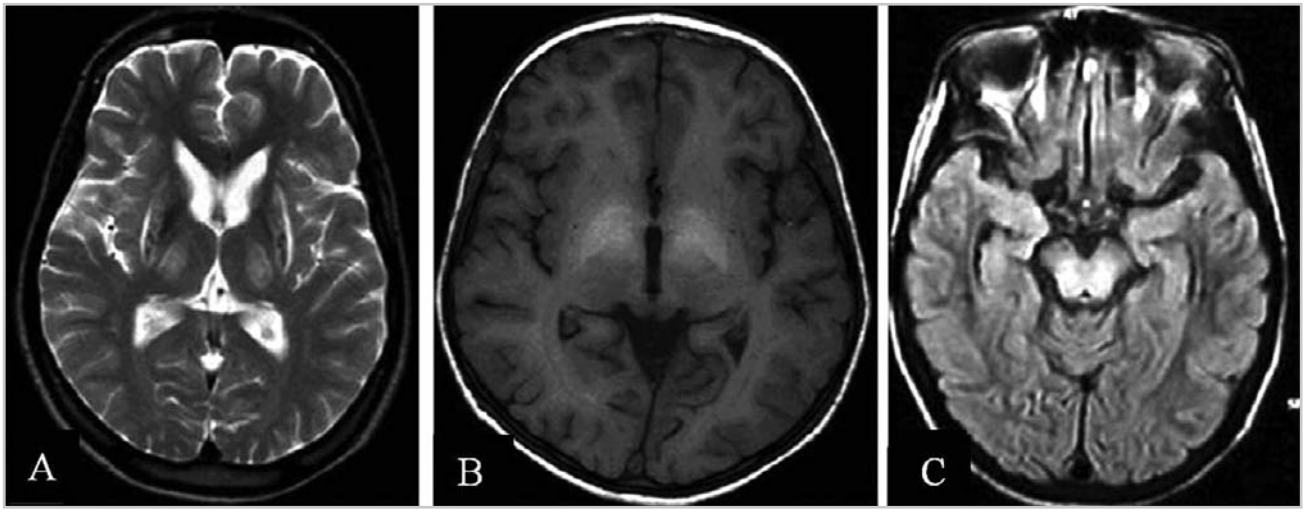

Figure 1: MRI brain A) T2 weighted image, B) T1 weighted image C) FAR image

unremarkable. On examination, vital parameters were normal.. The patient had pallor and bilateral pitting edema extending up to the knees. He was not icteric. Central nervous system examination showed normal higher mental functions; increased tone, brisk deep tendon reflexes and flexor plantar reflexes bilaterally. Dysdiadochokinesia, intentional tremors, spastic ataxic gait were present right more than left. Sensory and posterior column examination was normal. Other systematic examination was normal. A baseline investigation showed picture of pancytopenia (Hb -9.1gm/dl, Total Leucocyte Count -3100/mm3 and platelet count-1.1 lakh/mm3) and deranged coagulation profile (prolonged prothrombin and Activated Partial Thromboplastin Time). Liver function test revealed hypoalbuminemia (Serum Albumin- 2.1) with normal liver enzymes. Serum ammonia level was not elevated. Kidney function test was normal. Diabetes was under control (Random Blood sugar-134mg% and HbA1c-4.0). The serology for Human Immuno-defiency virus and hepatic viral markers including Hepatitis B were negative. Ultrasonography of abdomen revealed features suggestive of chronic liver disease and splenomegaly. CT Brain showed bilateral centrum semiovale hypodensities. In view of chronic liver disease with neurological symptoms, a differential diagnosis of Wilson disease was considered and the patient was worked up. Patient was then referred for an MRI-Brain scan which revealed hyper intense bilateral, symmetrical lesion in the basal ganglia on T2-weighted, T2 Flair images and hypo intense area on T1W images. Hyper intensity was also seen bilaterally in the frontal lobes near the orbital surface on diffusion weighted images. Cortical atrophy was also appreciated. MRI Brain showed multiple chronic ischemic foci in bilateral periventricular and adjacent fronto-parietal subcortical matter **(Figure 1)**. Serum ceruloplasmin was low at 10 mg/dl 24-Hour Urine Copper was 151ug/day (normal-32 to 64ug/day). The values were rechecked. Slit Lamp examination showed no Kayser-Fleischer ring. Liver biopsy was not done in view of deranged coagulation profile. Patient was diagnosed to have Wilson Disease with late-onset of neurological manifestations. The anemia and splenomegaly were explained as complications of the disease and portal hypertension. The patient and his relatives were counseled about the condition and the treatment options. The treatment was started with penicillamine (1 gm daily in divided doses) and high dose zinc (200 mg/day) as maintenance with pyridoxine 25 mg/day and dietary restrictions for copper which he was advised to continue on long term basis and showed improvements on follow up.

Discussion

Wilson's disease (WD) is a rare inherited autosomal recessive inborn error of copper metabolism characterized by toxic accumulation of copper in liver, brain, cornea and other tissues, manifesting either as neurological or psychiatric features or symptoms of liver disease. [4] The main etiology of WD is credited to the mutation in the ATP7B gene, located on chromosome 13. What makes this disease important is its diverse clinical presentation. Also, it may be fatal to the life of the patient, if it remains undiagnosed due to its progressive nature. [1] The onset of Wilson disease after 40 years of age is rare, although cases have been described of patients presenting in the fifth and sixth decades. [7,8] Neurological manifestations commonly appear in adolescence or early adulthood and include dysarthria, movement disorders, ataxia, and micrographia. An adolescent may have deteriorating performance in school or athletics. Onset of neurological symptoms in the elderly has been reported in a few cases. [11,12] Till the present date, no single test can exclude or confirm WD with 100% certainty . The diagnostic workup includes identification of corneal Kayser-Fleischer rings,

reduced serum ceruloplasmin and copper as well as a quantitative determination of liver copper concentration. [3,9,10] Kayser-Fleischer rings, located at the periphery of the cornea, consist of dense granules of copper and sulfur and are green-yellow or brown. These rings are a valuable diagnostic sign in patients exhibiting neurological and psychiatric disease because they are almost always present in these patients if they have Wilson disease. It is considered as one of the essential criteria for the diagnosis of Wilson disease [5]. When Wilson disease is considered a possible diagnosis, one of the best early tests is to measure 24-hour urine copper concentration, which is always elevated in symptomatic patients. The normal 24-hour concentration is 32-64 ug/d and symptomatic patients will always have > 100 ug/d. Rarely, a false-positive urine copper value may result because of obstructive liver disease [1] Magnetic resonance imaging (MRI) is an efficient method for documenting involvement of the central nervous system in Wilson's disease, thus allowing better anatomical and clinical correlations. [9]

Liver biopsy though considered as gold standard for the diagnosis of Wilson disease is not essential for diagnosis. [10] We present a rare case of Wilson disease with onset of neurological symptoms in the sixth decade without Kayser-Fleischer ring. Ross et al reported a patient with Wilson disease with onset of neurological symptoms at 58 years with precedent severe hepatic dysfunction and laboratory investigations. [11] Anil kumar T et al have reported atypical presentation of Wilson disease with late onset neurological disease without Kayser-Fleischer ring in Geriatric aged male [2] .Willet and Keichl reported a 23 year male with typical Wilson disease but no Kayser-Fleischer ring. [14] Demirkiran et al have reported a case of Wilson disease with neurological manifestation without Kayser-Fleischer ring in a 41 year old woman [6] Currently approved treatments for WD include penicillamine, zinc acetate and trientine. Recently Zinc and tetrathiomolybdate is considered as the treatment of choice for hepatic and neurologic manifestation of the disease respectively. Penicillamine is known to cause deterioration or onset of neurological disease in both presymptomatic and symptomatic patients. Our patient was treated with penicillamine (1 gm daily in divided doses) and high dose zinc (200 mg/day) with pyridoxine 25 mg/day which he was advised to continue on long term basis and showed improvements on follow up.

In conclusion, diagnosis of Wilson disease should be considered in the presence of hepatic and neurological symptoms even in the absence of Kayser-Fleischer ring irrespective of the age of onset.

References

1. Ala A, Walker AP, Ashkan K et al. Wilson's disease. **Lancet 369:** 397-408, 2007
2. Anil kumar T, Sudhir U, Priya Singal et al. Atypical Presentation of Wilson Disease without Kayser Fleischer Ring in Geriatric Age. **Al Ameen J Med Sci 3:** 251-254, 2010
3. Brewer GJ. Neurologically presenting Wilson's disease: Epidemiology, Pathos physiology and treatment. **CNS Drugs 19:** 185-192, 2005
4. Cuming JN. The copper and iron content of Brain and liver in the normal and in hepato lenticular degeneration. **Brain 71:** 410-415, 1949
5. Das SK, Ray K. Wilson's disease: an update. **Nat Clin Pract Neurol 2**: 482-493, 2006
6. Demirkiran M, Jankovic J, Lewis RA et al. Neurologic presentation of Wilson disease without Kayser-Fleischer rings. **Neurology 46:** 1040-1043, 1996
7. Ferenci P, Czlonkowska A, Merle U et al. Late-onset Wilson's disease. **Gastroenterology 132:** 1294-1298, 2007
8. Hefter H, Weiss P, Wesch H et al. Late diagnosis of Wilson's disease in a case without onset of symptoms. **Acta Neurol Scand 91:** 302-530, 1995
9. Panagariya A, Sureka RK, Sharma AK et al. Wilson's disease: A study of 21 cases from north-west India. **Ann Indian Acad Neurol 10:** 255-258, 2007
10. Pandit A, Bravedkar A, Bhave S. Wilson's disease. **Indian J Pediatr 69:** 758-791, 2002
11. Ross ME, Jacobson IM, Dienstag JL et al. Late-onset Wilson's disease with neurological involvement in the absence of Kayser-Fleischer rings. **Ann Neurol 17:** 411-413, 1985
12. Taly AB, Meenakshi-Sundaram S, Sinha S, Swamy HS, Arunodaya GR. Wilson disease: description of 282 patients evaluated over 3 decades. **Medicine (Baltimore) 86:** 112-121, 2007
13. Wilson SAK. Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver. **Brain 34**: 295, 1912
14. Willeit J, Kiechl SG. Wilson's disease with neurological impairment but no Kayser-Fleischer rings. **Lancet 337:** 1426, 1991