

## Neuro Wilson's – An Alien Presentation

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### ABSTRACT

Wilson's disease is an Autosomal recessive disorder of inborn error of copper metabolism in liver which results in accumulation of copper in the liver, brain, kidneys, eye and other organs affecting commonly children and young adults. Its incidence varied from 33 to 68 per 100,000 in India and 1 in 30,000– 40,000 in worldwide population. Mainstay of diagnosis primarily depends on clinical features, biochemical parameters, presence of Kayser-Fleischer (KF) ring. A middle aged man referred as spinocerebellar ataxia was incidentally found to be an exclusive case of Neuro Wilson's without involvement of the liver and hence we intend to report this case for its rarity.

**Keywords:** Wilson, Neuro Wilson, ATP7B gene, ceruloplasmin, 24-hour urinary copper, Kayser-Fleischer (KF) ring, giant panda sign, miniature panda sign, double panda sign, diffuse atrophy, putamen, external capsule.

### INTRODUCTION

Wilson's disease is a genetic disorder of inborn error of copper metabolism leading to accumulation of copper in the liver, brain, kidneys, eye and other organs commonly affecting the children and young adults. It was described by Kinnier Wilson, as one of the treatable fatal conditions when detected early. Beyond regular clinical presentation and imaging findings of such metabolic disorders, unusual, bizarre and overlapping presentation also to be born in mind for early identification of these inborn errors of metabolism and appropriate administration of anti-chelating therapy.

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### CASE REPORT

A 40 year old diabetic male patient presented in the outpatient department with history of on and off slipping of slippers and fall since 1 year. On clinical examination, he had ataxia and dysarthria. On CNS examination - tone and power was 5/5 on upper and lower limbs, but cerebellar signs were noted –ataxia, Romberg's test positive, dysidiadochokinesia, finger nose finger test positive, tandem walking. At the end of clinical examination, spinocerebellar ataxia was

suspected and patient was referred to the Radiology department for MRI brain and spine screening.

#### Lab Investigation

Complete hemogram, renal function and liver function test were within normal limits. Post prandial blood sugar was on higher side as the patient was diabetic.

#### MRI Brain:

The patient was subjected for a Magnetic Resonance Imaging (MRI) study using 1.5 Tesla Philips Intera machine with the following sequences - Sagittal: 3D T1WI TSE. Coronal: T2WI TSE. Axial: T2WI TSE, FLAIR, GRE/FFE, DWI/ADC.

Study showed bilateral, symmetrical T2WI and FLAIR hyper-intensities in putamen, caudate nucleus, external capsule, ventrolateral thalamus, mid brain and pons. [Figure 1, 2]

There are T2WI/GRE hypointense signal noted in the bilateral globus pallidus, superior colliculus and dentate nucleus representing mineral deposition. [Figure 3] On T1WI, the same appeared hyperintense – ruling out the possibility of iron and calcium deposits and suggesting copper deposition. [Figure 4]

There is typical T2WI hyper-intensity noted in the tegmentum of midbrain with relative sparing of the red nucleus, substantia nigra with hypo-intensity of superior colliculus – representing the face of Giant Panda sign [Figure 5].

There is also face of miniature Panda sign consisting of T2WI hypo-intensity in the central tegmental tracts with relative hyper-intensity of the aqueduct

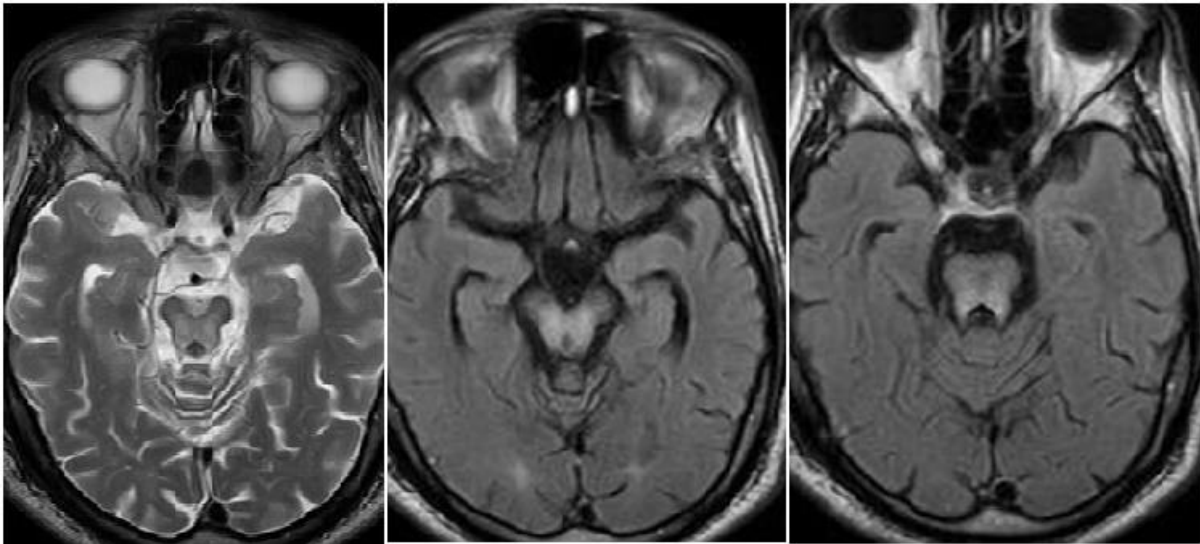


Figure 1: T2W/FLAIR hyperintensities noted in the midbrain and pons.

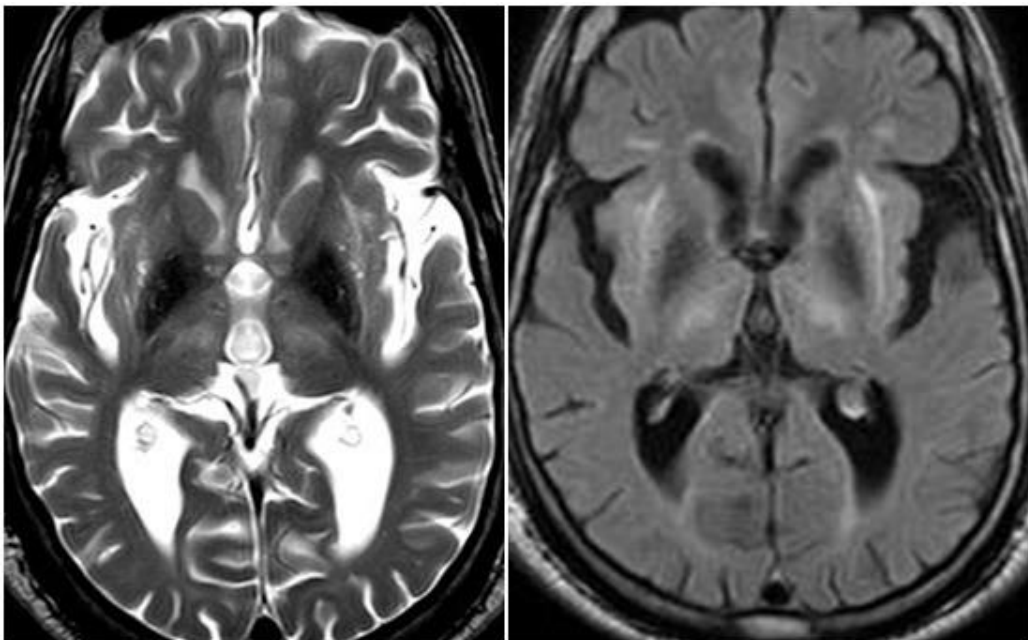


Figure 2: showing T2WI/FLAIR hyperintensities in the bilateral caudate nucleus, ventrolateral thalamus and putamen (PUTAMEN RIM SIGN).

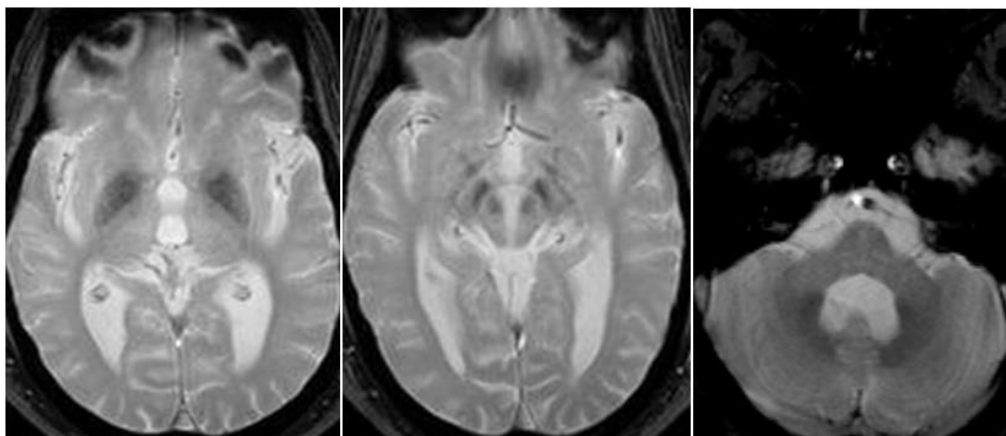


Figure 3: T2/GRE hypointensities noted in the bilateral globus pallidus, red nucleus, substantia nigra and dentate nucleus

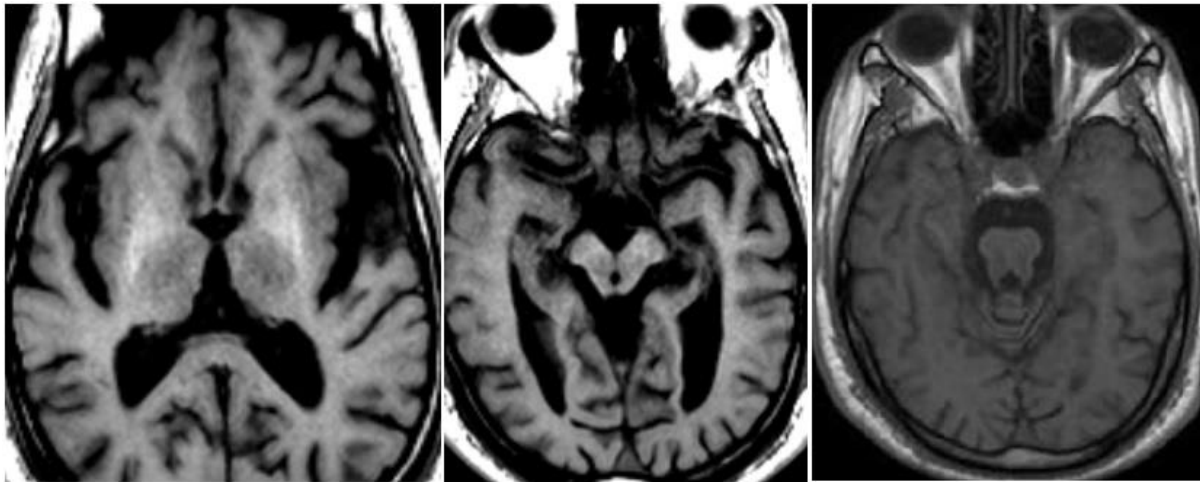


Figure 4: T1WI axial section shows hyperintensity in the putamen, globus pallidus, midbrain, pons – mineral (copper) deposition



Figure 5: T2WI axial section showing the FACE OF GIANT PANDA sign where there is hypointensity in the red nucleus and substantia nigra (eyes and nose of giant/ mother panda– appears black) with surrounding hyperintensity in the midbrain – s/o Wilson's disease

relative hyperintensity of the aqueduct opening into the fourth ventricle and superior cerebellar peduncles (nose and mouth of baby panda – appears white) – s/o Wilson's disease

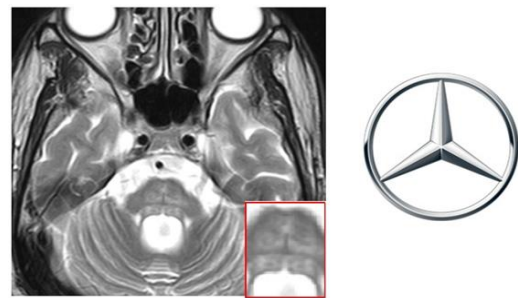


Figure 7: T2WI axial section showing the TRIDENT / MERCEDES sign where there is abnormal hyperintensity in pons with characteristic hypointensity – s/o Wilson's disease

opening into the fourth ventricle and superior cerebellar peduncles. [Figure 6]

Abnormal hyper-intensity noted in Pons with characteristic hypo-intensity in the middle forming a star shape in T2WI axial section showing the Trident / Mercedes sign. [Figure 7]

The patient also had evidence of diffuse cerebral, cerebellar, midbrain and Pontine atrophy. [Figure 8]



Figure 6: T2WI axial section showing the FACE OF MINIATURE PANDA sign where there is hypointensity in the central tegmental tracts and medial longitudinal fasciculus (eyes of panda) with

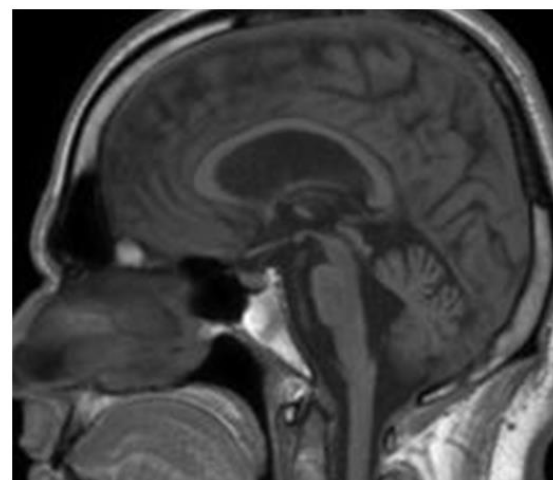


Figure 8: shows generalized atrophy of the midbrain, pons, medulla which occurs in fulminant condition of Neuro Wilson's disease.



### Spine Screening:

No altered signal intensity/atrophy of spinal cord were seen. Disc degeneration changes noted at lower cervical and L5-S1 level.

The **Differential Diagnosis** considered were Multisystem Atrophy (MSA), Neuro-degeneration with Brain Iron Accumulation (NBIA) and Wilson's disease.

Though there was generalized atrophy including Pons depicting Multisystem Atrophy (MSA), clinically patient did not have any autonomic dysfunction nor any cruciform hyper-intensity in the Pons on imaging showing the classical "Hot Cross Bun" sign but instead hypo-intensity was noted forming the Trident sign.

Similarly, there was suspicion of Neuro-degeneration with Brain Iron Accumulation (NBIA). Clinically patient did not have any extra-pyramidal symptoms or intellectual deterioration. Radiologically, mineral deposition displayed hypointense signal on all MR sequences except T1WI in which it appeared hyperintense, ruling out the possibility of the mineral being iron.

Hence, the diagnosis of Wilson's disease with extensive neurological involvement was suspected.

With this suspicion, ophthalmological examination, serum ceruloplasmin and 24-hour urinary copper excretion tests were done which showed Kayser-Fleischer (KF) Ring [Figure 9] in slit-lamp examination, low serum ceruloplasmin level (8.08mg/dl) and elevated 24-hr urinary copper excretion (101.18 µg/24hrs).

Further evaluation with abdominal sonography turned out to be normal with no significant change in liver echo texture or portal vein diameter.

Finally arrived at the diagnosis of **Fulminant variant of Neuro Wilson's disease** without any liver biopsy as serum ceruloplasmin levels was low, 24-hour urinary copper excretion was elevated and KF ring was present, which was considered as diagnostic criteria.<sup>[1,2]</sup> Patient was started on penicillamine therapy and patient showed mild improvement of symptoms.

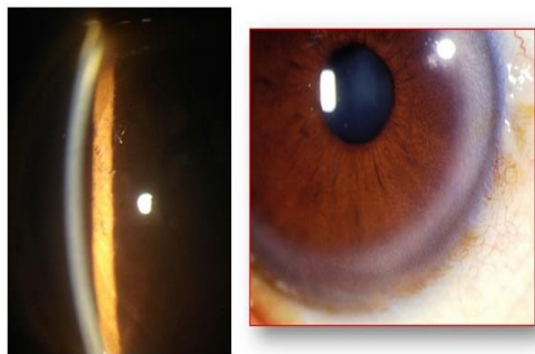


Figure 9: Showing Kayser -Fleischer ring in Descemet's membrane on Slit lamp and naked eye examination.

### DISCUSSION

Wilson's disease, also known as Hepatolenticular degeneration, is a rare autosomal recessive multisystem disorder, which is caused by a mutation in the copper-transporting gene, ATP7B that causes major pathological impact on liver though it is a generalized disease. Defect in this gene causes reduced incorporation of the copper in to ceruloplasmin, which is copper transport protein. There is excessive accumulation of copper in the liver and brain because of an inherited defect in the biliary excretion of copper by the ceruloplasmin. When the storage capacity of the liver for copper is exceeded or when copper cannot be transported inside the liver, levels of non-ceruloplasmin bound copper in the circulation are elevated and copper also accumulates in extra-hepatic sites, especially brain.<sup>[3]</sup> It was first described as Progressive lenticular degeneration by Kinnier Wilson, as one of the treatable fatal conditions when detected early. Its incidence varied from 33 to 68 per 100,000 in India<sup>[4]</sup> and 1 in 30,000 – 40,000 in worldwide population.<sup>[5]</sup> Though literature concentrates on copper deposition in liver and lentiform nucleus, it also affects other parts of brain presenting in a fulminant way. Most of the patients present in the second decade of life with a primary hepatic presentation, with the remainder of the patients present during the third and fourth decades, with a primarily neurologic or a psychiatric presentation.<sup>[6]</sup> In most of the Indian studies, the disease was found to manifest at a younger age in Indian children.

The earliest pathologic changes in the liver may consist of steatosis and distinctive mitochondrial changes. With progression, it ranges from chronic hepatitis to fulminant hepatic failure with architectural distortion. In brain, copper gets accumulated in the lentiform nuclei causing various degenerative changes. Same changes are also noted in the kidneys and eyes.<sup>[7]</sup> Kayser-Fleischer rings (KF rings), a pathognomonic sign, may be visible in the cornea of the eyes, either directly or on slit lamp examination in a ring fashion around the cornea. They are due to copper deposition in Descemet's membrane. KF rings occur in approximately 66% of diagnosed cases (more often in those with neurological symptoms rather than with liver problems). In kidneys, they present as renal tubular acidosis type 2. Biochemically there is increased liver enzymes, decreased ceruloplasmin levels and elevated 24-hour copper excretion levels.<sup>[8]</sup>

In Wilson's disease with neurological presentation, the symptomatology is dystonia, wing-beating tremors, dysphasia, dysarthria, ataxia, Parkinsonism like symptoms. The neurological symptoms are usually secondary to the cerebral copper deposition, which is sufficient to destroy the nerve cells. They also present in the later stage with psychiatric

symptoms like depression, neurosis, personality changes and psychosis.<sup>[9, 10]</sup>

Radiologically, numerous articles have dealt with the magnetic resonance (MR) findings of the brain in Wilson disease and the most common focal abnormalities have been found in the basal ganglia, especially in the lenticular nucleus. Studies published by Starosta-Rubinstein et al., van Wassenauer-van Hall et al., Svetel et al., had high signal intensity on T2W images of the basal ganglia, brainstem, cerebellar peduncles, and supratentorial white matter regions. Sener and van Wassenauer-van Hall et al study proved that high signal intensity on T2W images of the basal ganglia may represent edema, gliosis, necrosis and cystic degeneration, while high signal intensity of the white matter is most compatible with degeneration and spongy or cystic disintegration.<sup>[11]</sup> But later study done by Braffman found low signal intensity on T2W images of the globus pallidus, substantia nigra, red nucleus and corpus striatum.<sup>[12]</sup> Wilson's disease can also present as the increased signal, and/or the decreased size of the affected structure involving putamen, caudate, subcortical white matter, thalamus, globus pallidus, midbrain, and cerebellum. Grover et al described similar extensive involvement of the cortical and subcortical areas of the frontoparietal lobes with bilateral basal ganglia, thalami, midbrain and Pons in a 14 year old child who presented with neurological symptoms.<sup>[13]</sup> Previous Indian study by Jha et al revealed a 10% incidence of white matter involvement in patients presenting with neurological symptoms.<sup>[14]</sup>

The midbrain 'face of giant panda sign' is due to high signal in the tegmentum, normal signals in the red nuclei and lateral portion of the pars reticulata of the substantia nigra and hypo-intensity of the superior colliculus. The 'face of the miniature panda', or the 'panda cub' sign seen in dorsal pons, is delineated by the relative hypo-intensity of the medial longitudinal fasciculi and central tegmental tracts ('eyes of the panda') in contrast to the hyper-intensity of the aqueduct opening into the fourth ventricle ('nose and mouth of the panda') bounded inferiorly by the superior medullary velum. Together they form the 'Double Panda sign'.<sup>[10]</sup> Central pontine myelinolysis (CPM)-like changes have been described as trisected pattern – 'Trident / Mercedes-Benz sign'.<sup>[15, 16]</sup>

Our patient had neither a clinical nor a biochemical evidence of a hepatic involvement. But neurological involvement was widespread. There was diffuse and extensive involvement of brain including - putamen, caudate nucleus, external capsule, ventro-lateral thalamus, mid brain and pons with multiple areas of copper deposition- bilateral globus pallidus, superior colliculus and dentate nucleus seen as hyper-intensities in T1WI, with face of giant panda, miniature (baby) panda and trident signs along with

diffuse cerebral, cerebellar and brain stem atrophic changes at this age.

## CONCLUSION

Knowledge on Wilson disease is required while dealing adult patients with abnormal movements and neuro-behavioural abnormalities as it is easily treatable cause that are often missed which can prevent catastrophic outcome due to disease progression. Many pathognomonic neuro-imaging signs have been reported previously in literature, but generalized and extensive involvement of cerebral, cerebellar and brain stem and deep grey matter and simultaneous occurrence of the 'Double Panda' sign in midbrain and 'Trident' sign in Pons are a rare occurrence. Both these signs, which are characteristics of Wilson's disease, when occur simultaneously, significantly increase the likelihood of this diagnosis if the clinical setting is appropriate.

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