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Original Research Paper

Internal Medicine

A RARE PRESENTATION OF WILSON'S AMONG TWO SIBLINGS – A CASE REPORT

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ABSTRACT Wilson's disease (Hepatolenticular degeneration) is an inherited autosomal recessive disorder of copper metabolism that produces neurologic, psychiatric, and liver manifestations, alone or in combination. It is caused by mutations in the ATP7B gene encoding a P-type ATPase on chromosome 13q14.3. Manifestations of Wilson's disease are more likely to be hepatic in early childhood, and neurologic in adolescents and young adults. Neurologic onset usually manifests in the second decade of life with tremor, rigidity and dystonia. Here we are presenting two cases of WILSON'S disease manifesting as NEUROWILSON'S among two siblings of a family born out of secondary consanguineous marriage. Both the patients presented with history of difficulty in holding objects and history of tremors of both upper limbs and slurring of speech. Examination revealed a Wing beating tremor, Kayser Fleischer ring on slit lamp examination, low serum copper and low serum ceruloplasmin. Patients were treated with Penicillamine and Zinc acetate, discharged and advised regular follow up.

KEYWORDS : Wilson's Disease, Kf Ring, Wing Beating Tremor, Penicillamine, Zinc Acetate

INTRODUCTION:

Wilson disease (hepatolenticular degeneration) was first described in 1912 by Kinnier Wilson as a familial disease characterized by progressive, lethal neurologic dysfunction with liver cirrhosis and a corneal abnormality, the Kayser-Fleischer ring.[1] Wilson's disease is caused by loss-of-function variants in ATP7B. Mutations in ATP7B in Wilson disease impair both the incorporation of copper into apoceruloplasmin and the excretion of copper into bile, resulting in excess copper accumulation within hepatocytes.[2] Increased hepatic copper content combined with hepatocyte damage results in the release of copper into the blood. The increase in free serum copper presumably is the proximate cause of copper deposition and subsequent toxicity in the brain and other tissues. Urinary excretion of copper increases, but is not able to fully compensate for the decreased biliary excretion

Clinical manifestations include:

***Hepatic presentation*:**

jaundice, hepatomegaly, ascites, Edema

Neuropsychiatric:

Wilson's has varied presentations, which include

1. Dystonia (dystonia postures and choreoathetosis), Dysarthria, Facial grimace (Risus sardonicus), Drooling, Dysphagia, Dysgraphia,
2. Ataxia (ataxia with postural and intentional tremors)
3. Tremor (**wing beating**), seizures (rare).
4. Parkinsonism symptoms (hypokinesia, rigidity, resting tremors) [3]
5. Changes in personality (irritability, anger, poor self-control), depression, and anxiety

***Ocular Manifestations*:**

Kayser-Fleischer ring, a golden to greenish-brown band in the peripheral cornea (Descemet's membrane), sunflower cataract in the lens.

***Other manifestations*:**

Skeletal effects - osteoporosis and rickets, due to renal losses of calcium and phosphorus.

Hemolytic anemia - due to the direct toxic effects of copper on red blood cell membranes.

Renal - Fanconi syndrome

Biochemical Findings:

Low serum copper, Low serum ceruloplasmin, increased urinary copper excretion, Elevated liver enzymes, Hypoalbuminemia, Increased liver copper level.

Treatment options include copper chelation using drugs like D-penicillamine, Trientine hydrochloride, tetrathiomolybdate, drugs reducing copper absorption like Zinc acetate, Liver transplantation in patients unresponsive to medical therapy. Newer treatment modalities include gene therapy using adeno associated virus mediated ATP7B addition to hepatocytes.[1]

Case Presentation:

Case 1: (Elder sibling)

A 28 year old male presented with difficulty in holding objects with hands and tremors of both upper limbs since 6 months, slurring of speech since 6 months. Patient had past history of seizures and deformity of knee joints (knock knees) from 15 years of age.

On examination: Bilateral(right>left) high amplitude proximal coarse WING BEATING tremor is present. Knock knees are present, Tandem walking is impaired.

Case 2: (Younger sibling)

A 23 year old male presented with history of difficulty in using both upper limbs since 1 year - insidious in onset and gradually progressive in nature, history of slurring of speech since 1 year - insidious in onset and progressive in nature.

On examination: upper limb - high amplitude proximal WING BEATING TREMOR (left>right) bilateral striatal toes present, dysarthria - pauses with excessive stress on words is present. Slit lamp examination showed bilateral Kayser Fleischer ring is present in Descemet's membrane of both eyes.

Investigations –

INVESTIGATION	CASE 1	CASE 2
Haemoglobin	13.0g/dl	14.1g/dl
Serum bilirubin	0.8 mg/dL	0.64 mg/dL
AST	21IU/L	25
ALT	23IU/L	29
Serum creatinine	1.09	1.21
USG abdomen	Liver: normal in size and echotexture	Liver - normal in size and echotexture

SLIT lamp examination	No KF ring	KF ring present
Serum copper	32.52mcg/dL	42.73mcg/dl
Serum ceruloplasmin	0.13g/L	0.13g/L
Serum ionised calcium	1.1 mmol/L	1.24mmol/L
Serum Vit D3	11.8ng/ml	26.73ng/ml
Serum phosphorus	2.24 mg/dL	--
24hour urine copper	--	61 mcg/24hr

MRI Brain:
Bilateral symmetrical FLAIR AND T2 HYPER INTENSITIES IN THALAMUS, MIDBRAIN with sparing of red nucleus, peri aqueductal gray matter, dorsal pons and medulla suggestive of - WILSON'S DISEASE

Fig 1: Figure showing **KF ring** in Case 2, copper deposition over Descemet's membrane

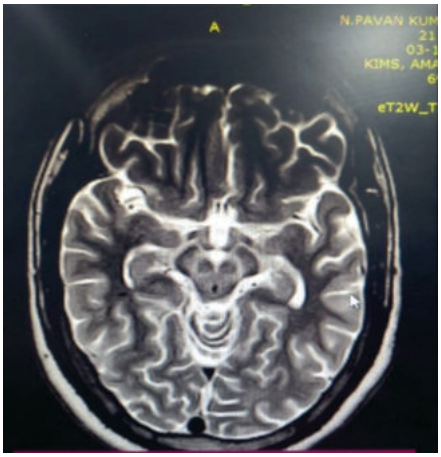

Fig 2 : T2 weighted MRI demonstrating **"Face Of Giant Panda Sign"**

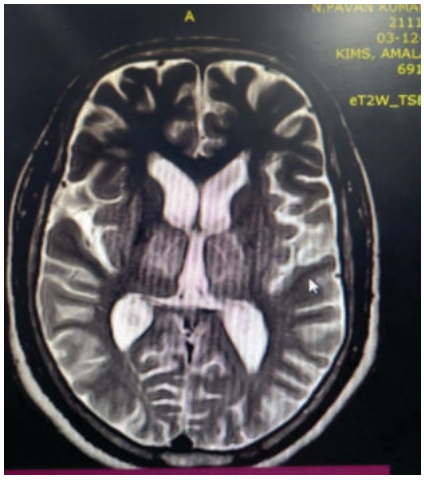

Fig 2 : T2 weighted MRI demonstrating **Hyperintensities In Bilateral Thalamus**

DISCUSSION:

Here, we have two patients of NEUROWILSON'S disease born out of a consanguineous marriage presented with wing beating tremor, dysarthria, elder sibling with past history of seizure and knock knees, younger sibling with KAYSER FLEISCHER Ring on slit lamp examination. On further investigation, both the patients had low serum copper and serum ceruloplasmin, and MRI BRAIN showing - Bilateral symmetrical FLAIR AND T2 HYPER INTENSITIES IN THALAMUS, MIDBRAIN with sparing of red nucleus, Peri Aqueductal gray matter, dorsal pons and medulla (PANDA SIGN)- s/o WILSON'S DISEASE.

Both the patients were treated with Penicillamine 250mg BD and Zinc acetate 220mg BD and supplemented with Pyridoxine, calcium and vitaminD3. Patient was instructed to avoid copper rich diet. Patient was discharged and advised regular follow up. Patient improved symptomatically within a span of 6-8 months and patients on maintenance therapy with ZINC and penicillamine.

CONCLUSION:

Wilson's disease is arguably one of the best-characterized human inborn errors of metabolism from combined clinical, biochemical, and molecular perspective, hence prompt diagnosis in the early symptomatic phase of the illness (or presymptomatic detection) and lifelong treatment are needed to avoid premature mortality in affected individuals.

The prognosis in patients with Wilson disease is excellent in all except those with advanced disease and those who present with rapidly progressive liver failure and haemolysis. In the absence of treatment, the course is progressive and leads to severe neurologic dysfunction and early death in the majority of patients, although a small proportion experience a relatively benign course.

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