

Rare Initial Presentation of Wilson's Disease as Acute Encephalopathy with Recurrent Seizure

Vinitha Leelamani^{1*} and Jacob George²

¹Department of Neurology, Sohar Hospital, Sohar, Oman

²Department of Neurology, Government Medical College, Kottayam, India

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ABSTRACT

Basal ganglia-based movement abnormalities are the hallmark of the neuropsychiatric presentation of Wilson's disease. Seizures are rarely reported in Wilson's disease, especially as the initial presentation. We report a case of a 17-year-old male who was admitted with recurrent seizures and initially treated as a case of encephalitis and on subsequent follow-up diagnosed with Wilson's disease. This case highlights the importance of considering the possibility of Wilson's disease in young patients presenting with unexplained encephalopathy.

Wilson's disease is attributed to a mutation in the *ATP7B* gene on chromosome 13 which causes an error in copper metabolism. The *ATP7B* protein is involved in the incorporation of copper into ceruloplasmin and its transport into the bile.¹ Neurologic dysfunction is the initial clinical manifestation of Wilson's disease in 40–60% of patients, with usual appearance at around 20 years of age, while initial hepatic manifestations are seen in 40–50% of patients with a slightly earlier age of onset.^{2,3} Wilson's disease with its varied clinical manifestations is a diagnostic challenge. Seizure is uncommon in Wilson's disease and its initial presentation as seizure is very rare.

CASE REPORT

A 17-year-old male was admitted with recurrent episodes of seizures. The patient had a low-grade fever for two days, a week prior to admission. He started to have visual hallucinations in the form of seeing things burning at a distance. On the night prior to admission, his parents heard a loud cry from his room and found him convulsing and he had six serial seizures. He was diagnosed as a case of acute encephalopathy with seizures and managed as status epilepticus.

The patient was evaluated for infectious and autoimmune causes for his condition. His cerebrospinal fluid study yielded normal results; cerebrospinal fluid viral markers were negative for

herpes simplex 1 and 2 and varicella zoster. N-methyl-D-aspartate receptor antibody was negative. He was given a course of acyclovir and methylprednisolone, followed by oral steroids. Though the patient made a gradual recovery in one week, he remained stubborn and irritable. Upon recovery, he was clinically normal without any neurologic deficits. Magnetic resonance imaging (MRI) of the brain showed multiple cortical hyperintensities and subcortical white matter hyperintensities [Figure 1]. Interictal electroencephalogram showed focal epileptiform discharges from the left frontal region.

The patient was discharged on steroids and sodium valproate as an antiepileptic. At the four-month follow-up visit to the neurology clinic, asymmetric tremors of the hands and dysarthria were noticed. Initially, this was suspected to be post encephalitis sequelae or due to drug effect. He was started on levodopa and trihexyphenidyl with which he made a mild improvement.

Five months after the first admission, the patient, who had been compliant with the prescribed medications and his steroid was being tapered, was readmitted with recurrent seizures. The seizure episodes were characterized by behavioral arrest, head aversion to the right, and drooling of saliva that lasted about a minute.

The patient was readmitted and his parents were again interviewed for any relevant past history. They revealed a slow decline in his school performance during the previous year, and that his handwriting had become much less legible [Figure 2]. There

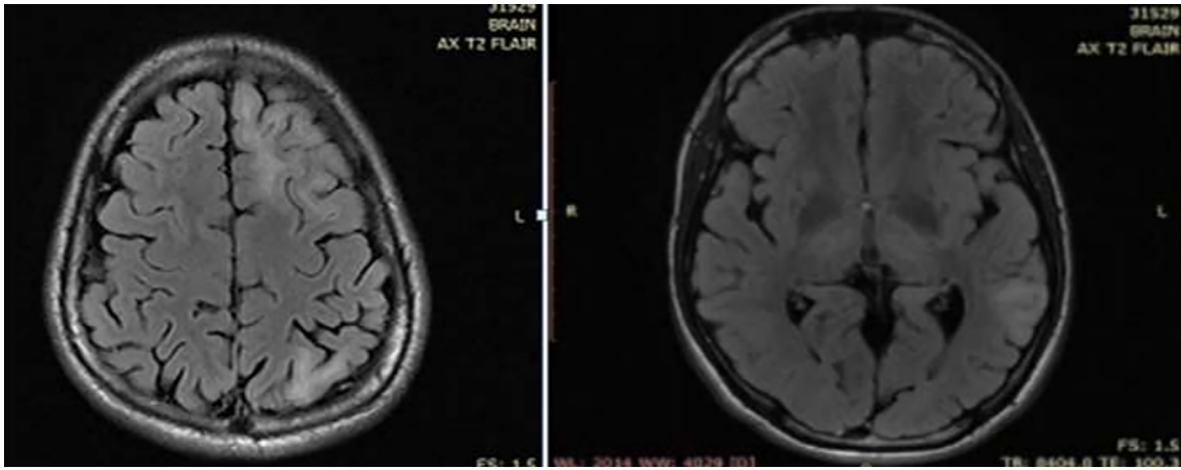


Figure 1: MRI of the brain showing multiple cortical and subcortical white matter hyperintensities.

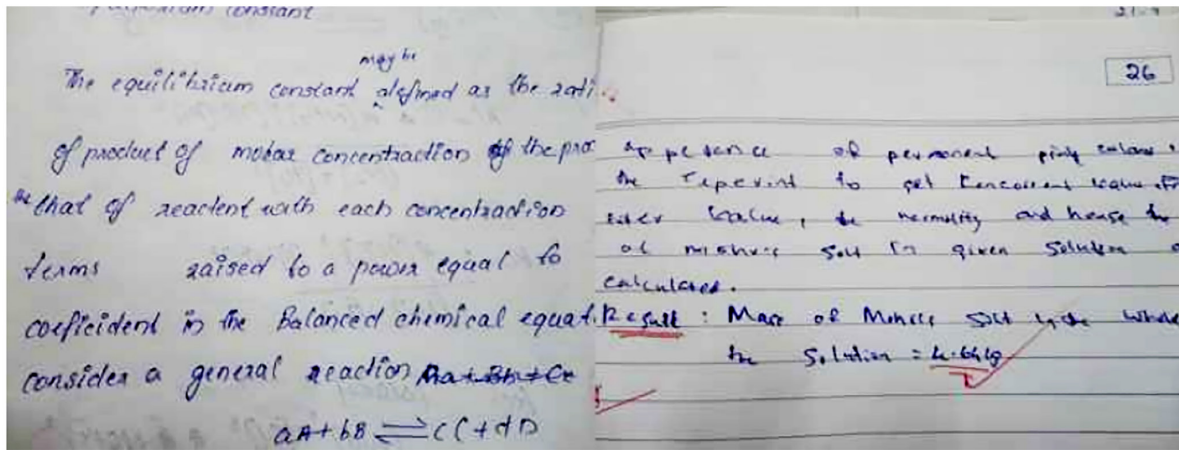


Figure 2: Handwriting sample before symptoms (left). Handwriting after one year, showing a decline in legibility (right).

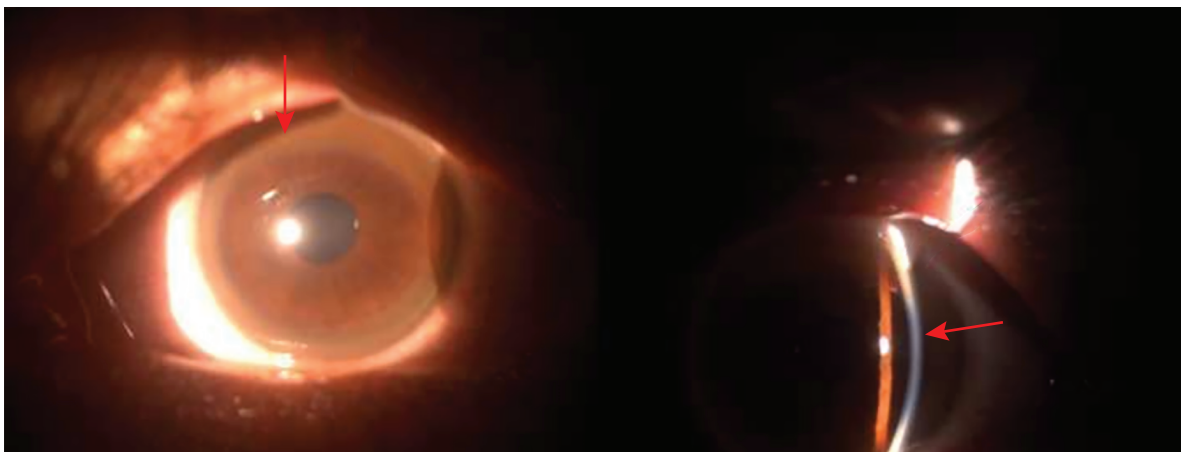


Figure 3: Slit lamp photograph of the patient's eye showing Kayser- Fleisher ring (red arrows).

was no relevant family history. His parents were non-consanguineous.

In view of the unusual presentation of mild parkinsonian symptoms and tremors in a young patient, he was reexamined thoroughly. Slit lamp

examination of the eyes showed Kayser-Fleischer rings [Figure 3]. Serum ceruloplasmin level was 3 mg/dL (in Wilson's disease it is < 20 mg/dL) and the copper content in 24-hour urine output was 103 mcg (> 100 mcg is diagnostic of Wilson's

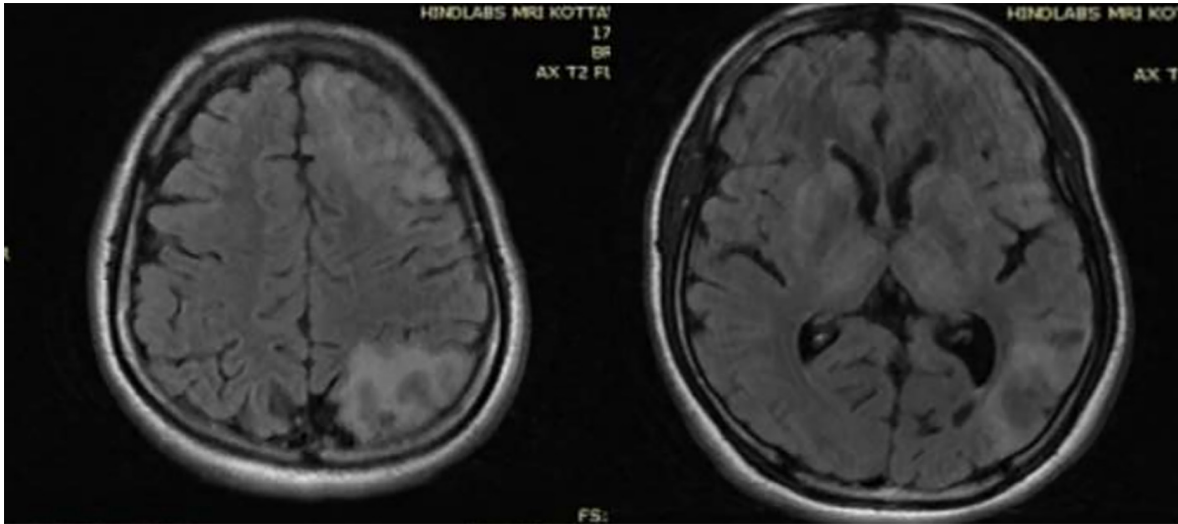


Figure 4: Follow-up MRI brain after six months showing T2 fluid-attenuated inversion recovery hyperintensities in white matter, as well as hyperintense lesions in bilateral basal ganglia and thalamus.

disease). Liver function test showed mildly elevated aspartate aminotransferase. Blood coagulation level was normal while hemoglobin was low (10 g/dL). Peripheral blood smear test yielded normal results. Ultrasound of the abdomen showed hyperechoic liver parenchyma and no cirrhosis. A follow-up MRI of the brain showed T2 hyperintensities in subcortical white matter, symmetric hyperintensities in the caudate, putamen, and thalamus [Figure 4].

Based on these results, Wilson's disease was confirmed in this patient. He was initially treated with zinc sulfate and then started on penicillamine with slow up-titration of the dose. As tremor and parkinsonian symptoms resolved, the antiepileptic doses were tapered to minimum. Currently (after six months of discharge), he is stable without recurrence of neurologic symptoms and is compliant with the prescribed long-term medications.

DISCUSSION

In Wilson's disease, the major neurological symptoms are extrapyramidal, the usual ones being tremors, dystonia, parkinsonism, dysphagia, and dysarthria. Chorea, athetosis, and myoclonus can also occur albeit rarely.^{4,5} Cerebellar dysfunction develops in approximately 30% of patients.⁶ Initial presentation of acute encephalopathy with seizures is rare. Only 8% of patients with Wilson's disease have seizures, 20% of whom would have had seizures before the onset of the characteristic features of Wilson's disease.⁷ Such seizures can be simple, complex,

partial, generalized tonic-clonic (the commonest form), secondary generalized, periodic myoclonus, or status epilepticus.⁷⁻⁹

The prognosis of seizures in Wilson's disease is positive, being rarely refractory. MRI imaging characteristics in Wilson's disease patients with seizures were similar to those without seizures.⁷ Seizure outcome is perhaps independent of the type of anti-epileptic drug used. There is no specific guideline as to which anti-epileptic drug is preferable.

The most characteristic abnormalities in Wilson's disease are increased signal intensity on T2-weighted images and reduced signal intensity on T1-weighted images in the basal ganglia, brainstem, and thalamus.¹⁰ The 'face of the giant panda sign' in the midbrain, the 'face of the miniature panda sign' in the pons, and the bright claustrum sign, while described, occur only rarely and thus are of limited diagnostic value. White matter signal changes can also be seen in Wilson's disease. The presence of subcortical white matter lesion, particularly the frontal lobe, is correlated with seizure.⁷ Seizures can occur at any stage of Wilson's disease—as the first symptom, at the initiation of treatment, during treatment, or as a terminal event. Electroencephalogram abnormalities include generalized and focal epileptiform discharge, diffuse or focal slowing of background activity, or periodic high voltage activity.⁷ The possible mechanisms for seizure in Wilson's disease include direct toxicity from accumulated free copper, pyridoxine deficiency due to penicillamine treatment, or metabolic encephalopathy.^{6,11}

Behavioral and psychiatric symptoms are common in Wilson's disease and may precede other symptoms. This may be in the form of declining school performance, impulsiveness, or psychotic features. Severe cognitive deterioration is rare and seen only in advanced cases.¹²

Serum ceruloplasmin is a readily available screening tool but can be normal in 5–15% of patients.³ Urinary copper levels are typically more than 100 mcg/dL in patients with symptomatic Wilson's disease. Free copper (non-ceruloplasmin-bound) will be elevated in serum. Liver biopsy is a sensitive and accurate test to diagnose Wilson's disease.¹³ In patients presenting with either neurologic or psychiatric dysfunction, a combination of Kayser-Fleischer rings, elevated 24-hour urinary copper, and reduced ceruloplasmin essentially confirms the diagnosis of Wilson's disease, thus precluding the need for liver biopsy.

Our patient's initial presentation was encephalopathy with seizures. It was the absence of classic manifestations of Wilson's disease early in the illness that led to a delay in diagnosis. Though rare reports of Wilson's disease presenting initially as seizure exist, initial presentations as acute encephalitis are rare. In our case, the parents did notice the slow decline in school performance and deterioration in handwriting, but they failed to report these early.

This case demonstrates the importance of detailed history taking and clinical examination in any neurologic or neuropsychiatric presentation, despite advances in imaging and electrophysiology. Wilson's disease should be considered in the differential diagnosis in young patients presenting with otherwise unexplained encephalopathy. Being a treatable disease, screening of Wilson's disease should be conducted in any atypical neurologic presentation. In the future, as genetic testing becomes ubiquitous, the current challenges and uncertainties in diagnosing this condition are likely to be resolved.

CONCLUSION

Wilson's disease is treatable albeit challenging to diagnose and should be considered in the differential diagnosis of any unexplained neurologic or psychiatric dysfunction, particularly in young patients.

Disclosure

The authors declared no conflicts of interest. Informed written consent was taken from the patient and his kin.

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