CASE REPORT

Difficulties in Diagnosis of Neurological Manifestations of Wilson Disease

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ABSTRACT

An uncommon disease due to altered copper metabolism, Wilson disease primarily involves the basal ganglia and liver, and affects males and females equally. Diagnosis of Wilson disease may be difficult, requiring blood and urine tests, and may include a liver biopsy. Copper chelation with penicillamine or trientine, oral zinc, and a low copper diet are recommended therapies.

We report the case of a 32-year old man who presented with 6-month history of gradual onset, progressively worsening history of aphasia with loss of comprehension, inappropriate vocalizations, increased aggression, and disturbed sleep. The patient had been exhibiting speech abnormalities, wherein his speech patterns and utterances became socially inappropriate and unrelated to the context, making it difficult for him to understand and communicate effectively.

A differential diagnosis including auto-immune and infectious encephalitis, neurodegenerative disorders like Creutzfeldt-Jakob disease (CJD) and Wilson disease was made. MRI Scan Brain (with FLAIR) showed T2WI hyper-intense signals in bilateral basal ganglia, brain atrophy, hyper-intense signals in periventricular, cortical, and sub-cortical regions. CSF analysis showed TLC 74 cells/uL with 90% lymphocytes, RBC 0 cells/uL, Protein 62 mg/dl and Glucose 69 mg/dl with no organisms on Giemsa stain and AFB stain microscopy. GeneXpert-PCR for MTB was also negative. His blood, urinary and spinal fluid cultures did not grow any organism growth. Serum cerulopasmin level was normal at 23 mg/dl. CSF autoimmune profile was negative. However, his 24-hour urinary copper was raised at 1201.8 ug (normal value 20-40 ug). Diagnosis of Wilson disease was made and he was started on pencillamine and zinc sulfate.

Key Words: Ceruloplasmin, copper, MRI brain, penicillamine, wilson disease

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INTRODUCTION

Primarily affecting the liver and basal ganglia in the brain due to altered copper metabolism, Wilson disease is inherited through autosomal recessive fashion[1]. The genetic defect in Wilson disease is localized at the long arm of chromosome 13 (13q) which alters copper transporting ATP gene. Affecting females and males equally, age of presentation usually ranges from four to forty years. Liver dysfunction is seen in the first decade of life in most Wilson disease patients. Hepatic symptoms include jaundice, vomiting, ascites, weakness, pedal edema, and skin itching. Neurologic and psychiatric features are more frequent in third and fourth decade of life. Neurological symptoms include speech abnormalities, tremors, personality changes, muscle stiffness, depression, anxiety and hallucinations[2,3].

If not diagnosed timely and treated promptly, Wilson disease can be fatal. Diagnosis of Wilson disease may be difficult, requiring blood and urine tests, and may include a liver biopsy. Genetic testing to screen family members of those affected has also been advised. Chelation of copper with penicillamine or trientine is the mainstay therapy in Wilson disease but may take 3-6 months to start working[4]. Oral zinc competes with copper for absorption at metallic ion transporter and is also prescribed. A low copper diet is advised with avoidance of chocolate, liver, mushrooms, shellfish, dried fruit and nuts. In neurological disease,

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physiotherapy and occupational therapy are also recommended.

Case Presentation

A previously healthy 32-year old gentleman presented with 6-month history of gradual onset, progressively worsening history of dysphasia, dysarthria, inappropriate vocalizations, drooling of saliva, increased aggression, and disturbed sleep. The patient had been exhibiting speech abnormalities, wherein his speech patterns and utterances became socially inappropriate and unrelated to the context, making it difficult for him to communicate effectively. There was a history of five episodes of generalized tonic-clonic fits in the last three weeks. Each fit occurred for 3-5 minutes in duration and was associated with urinary incontinence, frothing of saliva, and post-ictal confusion remaining for approximately up to 15 minutes. No history of trauma, fever, headache, dizziness, oral or genital ulcers, respiratory infections, sinusitis, skin rashes, joint pains, dysphagia, or hearing loss was recorded.

A shopkeeper by profession, he was married with two children and did not smoke or use illicit drugs. He was unable to work in the last four months due to his illness. There was no significant past history or family history of any similar disorder. On examination, he was fit-free having normal vital signs but no jaundice, pallor, clubbing or flapping tremors. On neurological examination, there was dysphasia and dysarthria with intact comprehension. Pupils were equally round and reactive to light with normal extraocular muscle movements. No nystagmus was found and fundoscopy revealed normal optic disc with no signs of papilledema. Slit-lamp examination did not reveal Kayser-Fleischer rings. There was drooling of saliva but no facial asymmetry with normal midline tongue and uvula. Signs of neck rigidity (Kernig and Brudzinski) were negative. There was generalized muscle rigidity but no focal sensory, motor, or cerebellar neurological deficit. There was flexor response to plantar reflex bilaterally and deep tendon reflexes were normal in all four limbs. Neither any viscera nor ascites were present clinically on abdominal examination. Respiratory and precordial examinations were normal.

A differential diagnosis included auto-immune and infectious encephalitis, neurodegenerative disorders like Creutzfeldt-Jakob disease (CJD) and Wilson disease. On investigation, CBC was normal TLC with normal ESR and CRP. His RFTs, LFTs and urinalysis were within normal parameters.

As shown in Figure 1, MRI Scan Brain (with FLAIR) showed T2WI hyper-intense signals in bilateral basal ganglia, brain atrophy, hyper-intense signals in periventricular, cortical, and sub-cortical regions. A

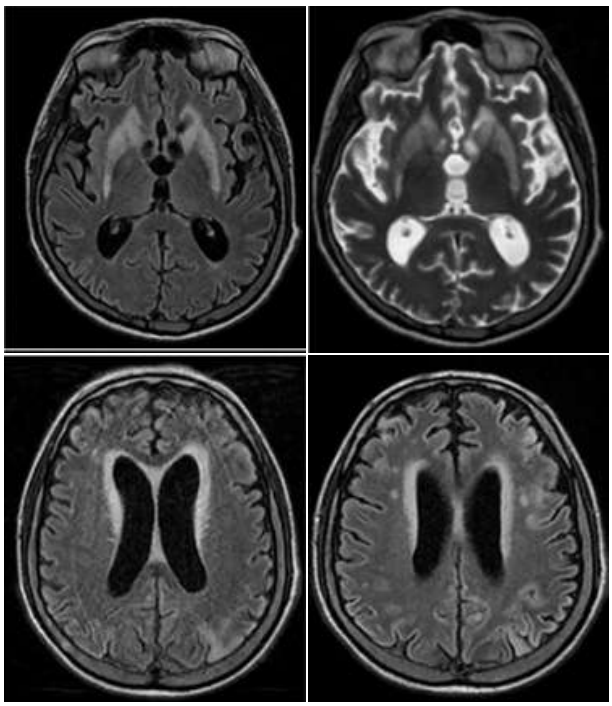

Fig. 1: MRI Scan Brain (with FLAIR) showing T2WI hyper-intense signals in bilateral basal ganglia, brain atrophy, hyper-intense signals in periventricular, cortical, and sub-cortical regions

lumbar puncture for CSF analysis was done. CSF analysis showed TLC 74 cells/uL with 90% lymphocytes, RBC 0 cells/uL, Protein 62 mg/dl and Glucose 69 mg/dl with no organisms on Giemsa stain and AFB stain microscopy. GeneXpert-PCR for MTB was also negative.

His blood, urinary and spinal fluid cultures did not grow any organism growth. Serologies for HBV, HCV, HIV and syphilis were negative. Serum cerulopasmin level was normal at 23 mg/dl. His echocardiography, chest X-ray, and abdomen ultrasound scan were within normal parameters. After sending CSF for autoimmune work-up, he was started on intravenous methylprednisolone 1000mg/day on lines of autoimmune encephalitis. There was no clinical improvement.

CSF autoimmune profile (including anti-NMDA receptor antibodies, anti-CASPR2 antibodies, anti-glutamate receptor antibodies, anti-DPPX antibodies and anti-GABAb receptor antibodies) was negative. However, his 24-hour urinary copper was raised at 1201.8 ug (normal value 20-40 ug). He was diagnosed as having Wilson disease and started on penicillamine and oral zinc sulfate. Additionally, physiotherapy and occupational rehabilitation were also planned. On follow up at three months, he was tolerating medicines without any adverse effects. His dysarthria, dysphasia and improper vocalizations had improved partially while aggression and drooling had settled completely.

DISCUSSION

In 1912, Wilson first described clinical presentation of 12 patients with neurological manifestations of Wilson Disease including drooling, movement disorders, dysarthria and psychiatric symptoms. Up to 50% patients with neurologic symptoms have co-existing liver cirrhosis. Neurologic manifestations usually develop as a consequence of untreated disease, treatment failure, poor compliance with copper chelation therapy or in patients with misdiagnosed liver disease and in patients with clinically silent hepatic stage[5].

MRI scan of brain is the most widely used neuro-imaging modality to aid in diagnosis of Wilson disease and rule out other causes. More than 90% patients of Wilson disease with neurological manifestations have MRI findings including symmetric T2WI hyper-intensities in the deep grey matter nuclei, basal ganglia, putamen, caudate nucleus, anterolateral thalamic nuclei, mesencephalic and pontine white matter[6,7]. It should be noted that these T2WI hyper-intense lesions may be reversible with copper chelation therapy and reflect edema and demyelination due to copper toxicity[8]. Ultimately, brain atrophy may develop and may be irreversible. Atrophy is seen in 30-45% of newly diagnosed Wilson disease patients with neurological manifestations and appears to be more common in men. Partial improvement in atrophy with copper chelation has been reported[9].

No single unanimously reliable non-invasive investigation is available to diagnose Wilson disease. Levels of serum ceruloplasmin, serum copper and urinary copper excreted during a 24-hour period are used to aid diagnosis. The gold standard for diagnosis is a liver biopsy[4]. Hepatic impairment, Kayser-Fleischer ring and abnormal serum ceruloplasmin level are frequently seen in Wilson disease but are not present in all the cases[4]. In the present case, elevated 24-hour urinary copper alongwith MRI brain findings were used to establish diagnosis of Wilson disease.

The present case highlights the difficulties in diagnosis of Wilson disease. Our patient presented with neuropsychiatric complaints in the fourth decade of life. There was no current or past history of liver involvement. At the time of assessment, there was no jaundice, Kayser-Fleischer rings, hepatosplenomegaly or ascites. His LFTs and serum cerulopasmin level were also normal. MRI Scan Brain (with FLAIR) showed T2WI hyper-intense signals in bilateral basal ganglia, brain atrophy, hyper-intense signals in periventricular, cortical, and sub-cortical regions. However the 24-hour urinary copper levels were markedly elevated and helped to establish the diagnosis.

In conclusion, high clinical suspicion is necessary to diagnose Wilson disease so that timely diagnosis and adequate treatment may be instituted to improve prognosis in these patients.

Conflict of interest: The authors declare no conflict of interest.

Authors' Contribution: NIB, MSAG and SS: Conceived and designed the study. NIB, MBR, and MMA: Did the initial literature research. MSAG and FA: Did the data collection, assembly and patient assessment. NIB, MBR and SS: Manuscript writing. MSAG, FA and MMA: Did the final critical review and corrections.

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