



Wilson's Disease presenting as Resistant Depression

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ABSTRACT

Introduction: Wilson's disease (WD) is rare, but it commonly presents with a variety of psychiatric symptoms.

Case report: A 31-year-old male presented with depression as the earliest manifestation. The depressive symptoms showed limited response to conventional antidepressants and electroconvulsive therapy in spite of compliance. Gradually, the patient showed neurological symptoms like motor slowing, speech disturbances, and abnormal movements which gave a clue toward organic etiology. Laboratory and neuroimaging findings along with ophthalmological examination helped in confirmation of diagnosis of WD. Introduction of the chelating agent penicillamine led to improvement in nonpsychiatric as well as psychiatric symptoms.

Conclusion: Psychiatric manifestations are common in WD. Depression was the earliest manifestation in our patient, which was not responding to usual treatment. Workup for organicity helped to diagnose WD and patient's depressive symptoms responded to chelating therapy.

Keywords: Depression, Neuropsychiatric interface, Wilson's disease.

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INTRODUCTION

Wilson's disease, which is also known as hepatolenticular degeneration, is an autosomal recessive disorder characterized by multiple mutation of gene ATP7B on chromosome 13q14.3 which is critical for hepatic copper excretion. Disturbances in copper metabolism result in copper accumulation in many tissues (brain, liver, and cornea), affecting the function of these organs. Though copper accumulates in all brain regions, pathological changes are mainly localized in the basal ganglia in the

brain. As a result of this, psychiatric and behavioral abnormalities are frequently seen in WD, and are often the initial manifestations of this disease. The estimates of psychiatric manifestation range from 30 to 100% of symptomatic patients. Various types of psychiatric morbidity are seen in patients with WD, of which depression is the commonest, affecting 30 to 60% of patients.¹

One-third of patients with WD initially present with behavioral abnormalities, and failure to recognize these may lead to misdiagnosis and delay in starting specific treatment.² Nearly 20% of patients undergo psychiatric treatment before specific chelation therapy begins.³

CASE REPORT

A 31-year-old male patient came with complaints of gradual onset of withdrawn behavior, irritability, sadness of mood, and fatigue since 1 year. Patient stopped going to work due to decreased interest and concentration in work. Also, there was a history of marital disharmony followed by separation due to his irritability and change in behavior. Patient was taken to a private psychiatrist where a diagnosis of major depressive disorder was made and the patient was started on antidepressants (combination of different classes of antidepressants in optimum doses). In view of nonimprovement of depressive symptoms, patient was administered 10 electroconvulsive therapy. Still there was no improvement. So the patient discontinued medications due to side effects, such as excessive sedation. He was without medication for about 6 months when the symptoms gradually worsened and he presented to our institute for further management.

On detailed history taking, patient's mother said that she has observed tremulousness and leaning of body backward while sitting by her son for last few months. She also reported that he had started speaking slowly and his speech had become slurred.

On neurological examination, the patient was conscious with dystonic posturing of back and grimacing facial movements. His cranial nerves and funduscopy were normal. There was hypertonia involving all four limbs, slurred speech, and bilateral brisk deep tendon reflexes.

On mental status examination, patient had psychomotor retardation, with grimacing and mannerisms. His mood was sad with restricted affect. Ideas of helplessness, hopelessness, and death wishes were expressed.

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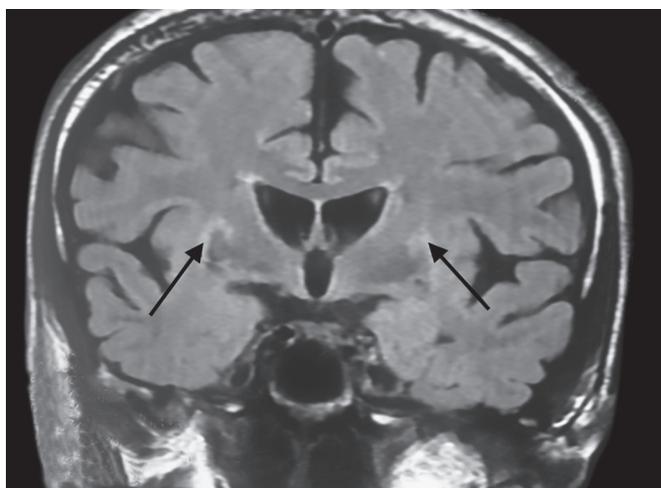


Fig. 1: Magnetic resonance imaging brain (plain) showing gliosis with calcification in bilateral basal ganglia

In view of his recently developed neurological symptoms, a neurological opinion was sought. Neurologist referred patient for laboratory and neuroimaging evaluation. Investigations revealed raised liver enzymes and high urine copper levels (48.30 $\mu\text{g}/\text{dL}$ normal up to 40 $\mu\text{g}/\text{dL}$). Hemogram, thyroid function tests, renal function test, and serum B12 levels were normal. Magnetic resonance imaging (MRI) brain showed gliosis with calcification in bilateral basal ganglia (Fig. 1). Suspicion grew toward possibility of an organic movement disorder like WD. For confirmation of diagnosis, patient underwent ophthalmological examination which showed Kayser Fleischer ring (KF ring) in both eyes (Fig. 2).

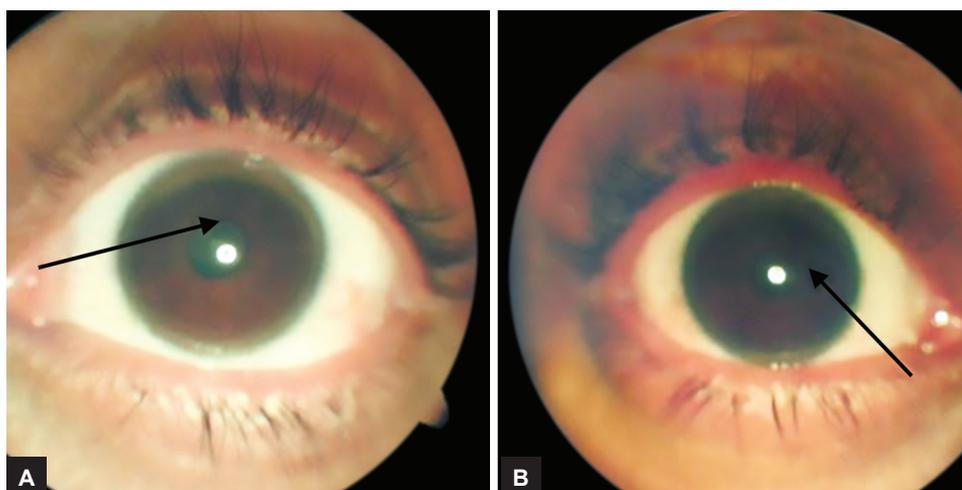
In view of depressive features not responding to the conventional antidepressants, gradual onset of neurological signs and symptoms and supportive laboratory, neuroimaging, and ophthalmological findings, patient was diagnosed as WD and started on penicillamine in a neurology inpatient setting. Patient's depressive symptoms responded to the chelation therapy gradually.

DISCUSSION

Neurology and psychiatry have evolved as two different specialties over a period of time, with neurology dealing with the structural aspect and psychiatry dealing with functions of the mind. However, in clinical practice, a significant overlap of symptoms in various neurodevelopmental and neurodegenerative conditions like multiple sclerosis, dementia, schizophrenia, and WD is seen. Clinical manifestations of WD are the result of gradual accumulation of free copper in the tissues, which may cause damage in many organs. Early manifestations are hepatic (40% of cases), neurological (35%), psychiatric (10%), and others (15%) like hematologic, renal, ocular.⁴ Neuropsychiatric symptoms in WD occur due to copper accumulation in basal ganglia and prefrontal cortex. Proposed biological mechanisms are reduced striatal dopamine and tyrosine hydroxylase levels and reduced dopamine D2 receptor density.⁵

Epidemiologically, WD is a disease of young age with slightly high prevalence in males who are also more likely than females to have neuropsychiatric symptoms.⁶ This can be attributed to difference in gender-related pathology in brain and may be explained by both estrogen neuroprotective effects and differences in brain iron metabolism. In the brain, estrogens act (1) as neurotrophins for dopaminergic neurons; (2) as antioxidants to protect cells against toxic metabolites; and (3) in dopamine synthesis, affecting uptake and dopamine receptor expression (decrease of D2 receptors and increase of the dopamine transporter density).⁷ This "estrogen protective hypothesis" can explain low prevalence of neuropsychiatric symptoms in females as compared with males in various neurodegenerative disorders including WD.

Psychiatric and behavioral abnormalities are common in the 5 years prior to diagnosis. Clinical features include loss of emotional control (angry outbursts and bouts of



Figs 2A and B: Ophthalmological examination showing bilateral KF ring

crying), depression, hyperactivity, loss of sexual inhibitions, anxiety disorders, cognitive impairment, mental retardation, mania, behavioral abnormalities, personality changes, and alcohol abuse.⁸ Most studies have shown that depression is predominant at the time of onset of the disease.^{1,8}

Accompanying neurologic symptoms are usually subtle and include tremors, speech difficulties, and micrographia. Most common neurological manifestations include postural and intentional tremors, dysphagia and contractions of facial muscles, dysarthria, bradykinesia, muscle hypertonia and choreathetoid movement of limb.⁹ Our patient presented with predominant mood and personality change and only on enquiry, his mother reported neurological symptoms—tremors, speech difficulty, and dystonic posturing of his back while sitting.

Diagnosis of WD is based on detailed evaluation and investigations. The laboratory findings show abnormal liver function tests (like raised liver enzymes), elevated urine copper (more than 40 µg/dL), high 24 hour urine copper (normal: 15–60 µg/24 hours), decreased blood ceruloplasmin levels, and increased copper levels on liver biopsy (>150 µg/gm). Similar findings were seen in our patient. In these patients, MRI of the brain shows hyperintensities in basal ganglia in the T2 setting. The KF ring is the single most important diagnostic sign in WD.¹⁰

In management, the mood disturbances show limited response to antidepressants in an optimum dosage and duration. Depressive symptoms in WD are probably due to the presence of both pre- and postsynaptic dopaminergic damage.⁵ Introduction of the chelating agent has been observed to be useful in normalization of mood and improvement in nonpsychiatric symptoms.¹¹

CONCLUSION

Wilson's disease commonly presents with psychiatric symptoms. Our case describes a patient presenting

primarily with depressive features. Poor response to antidepressants, excessive sensitivity toward psychotropic medications with gradually evolving neurological symptoms, and signs supporting investigations pointed toward WD. This case is presented to highlight the fact that a psychiatrist needs to be vigilant about psychiatric illnesses caused by underlying neurological diseases.

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