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When Copper Leaves Its Footprints: Characteristic MRI Patterns in Wilson Disease - A Case Report and Literature Review

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Abstract: ***Background: Wilson disease (hepatolenticular degeneration) is an autosomal recessive disorder of copper metabolism caused by mutation of the ATP7B gene, resulting in pathological copper accumulation in the liver, brain, cornea and other organs. Its estimated prevalence is approximately 1 in 30,000 individuals. Neurological manifestations, chiefly involving the basal ganglia, produce a wide spectrum of movement and psychiatric disorders, and the variable clinical presentation frequently mimics other conditions, leading to delayed diagnosis. Case Presentation: We report the case of a 15-year-old male who presented with poor scholastic performance, dysarthria, involuntary hand movements, abnormal gait, depression and episodic aggression, with a family history of a similarly affected elder sibling who died undiagnosed. Examination revealed a characteristic clown-like facies with risus sardonicus, and slit-lamp examination confirmed bilateral Kayser–Fleischer rings. Serum ceruloplasmin was markedly reduced (<7 mg/dL). Magnetic resonance imaging of the brain demonstrated symmetric T2/FLAIR hyperintensities involving the putamen, caudate nuclei, thalami, dorsal midbrain, dorsal pons and splenium of the corpus callosum, without diffusion restriction or susceptibility blooming, along with diffuse cerebral and cerebellar volume loss. Conclusion: MRI is a sensitive and specific tool for detecting neurological involvement in Wilson disease. Symmetric basal ganglia and brainstem T2/FLAIR hyperintensities are the most consistent imaging findings, and diffusion-weighted imaging helps in staging disease activity. Correlation of imaging with clinical, ophthalmological and biochemical parameters allows early diagnosis, timely chelation therapy and improved neurological outcome.***

Keywords: Wilson disease; hepatolenticular degeneration; basal ganglia; Kayser–Fleischer ring; diffusion-weighted imaging; magnetic resonance imaging; ATP7B

1. Introduction

Wilson disease is an inherited disorder of copper transport caused by mutations in the ATP7B gene located on chromosome 13q14.3, which encodes a copper-transporting P-type ATPase expressed predominantly in hepatocytes. Loss of function of this transporter impairs biliary copper excretion and incorporation of copper into ceruloplasmin, leading to progressive accumulation of free copper, first within the liver and subsequently in the brain, cornea, kidneys and other tissues.

The disease has a worldwide prevalence of approximately 1 in 30,000 individuals, with a higher carrier frequency in certain consanguineous populations. Hepatic manifestations range from asymptomatic transaminase elevation to acute liver failure and cirrhosis, whereas neurological disease typically presents in the second or third decade of life with a movement disorder (dystonia, tremor, parkinsonism, chorea), dysarthria, drooling, and behavioural or psychiatric disturbances such as depression, personality change and cognitive decline. Because the clinical picture is protean and overlaps with numerous other metabolic, infective and psychiatric conditions, diagnosis is frequently delayed, which carries a significant risk of irreversible neurological injury.

Neuroimaging, particularly MRI, plays a pivotal role in raising diagnostic suspicion, evaluating the extent of central nervous system involvement, and monitoring response to chelation or zinc therapy. The present case report describes the clinical, ophthalmological, biochemical and characteristic MRI findings in a young patient with neurological Wilson disease, and reviews the pertinent imaging literature.

2. Case Report

Clinical History and Examination

A 15-year-old male was brought with a six-month history of deteriorating school performance, dysarthria, involuntary movements of both hands, and an abnormal, unsteady gait. The family also reported behavioural changes including low mood and episodes of aggression. Family history was notable for an elder sibling with a similar undiagnosed illness who had died. There was no antecedent history of jaundice, overt liver disease, toxin exposure, or other identifiable metabolic disorder.

On examination, the patient had a characteristic “clown-like” facies with risus sardonicus (a fixed, vacant grin due to dystonic facial musculature) and dysarthric speech. Neurological examination revealed generalized dystonia and tremor. Slit-lamp examination by ophthalmology confirmed

bilateral Kayser–Fleischer rings – golden-brown deposits of copper in the Descemet membrane at the corneal limbus (Figure 1E).

Laboratory Investigations

Serum ceruloplasmin was markedly reduced at less than 7 mg/dL (normal range approximately 20–35 mg/dL), strongly supportive of a diagnosis of Wilson disease when interpreted together with the clinical and ophthalmological findings.

Imaging Findings

Magnetic resonance imaging of the brain was performed, including axial T2-weighted, FLAIR, diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) mapping, and gradient-recalled echo (GRE) sequences. The study demonstrated bilateral, essentially symmetric T2/FLAIR hyperintensities involving the putamen and caudate nuclei, the lateral thalami, the dorsal midbrain, the dorsal pons, and the splenium of the corpus callosum (Figure 1, panels A–D). No corresponding diffusion restriction was identified on DWI/ADC mapping, and no susceptibility blooming was seen on GRE imaging, a pattern consistent with the chronic stage of the disease. Diffuse cerebral and cerebellar volume loss with mild ventricular dilatation was also noted, in keeping with longstanding neurodegeneration.

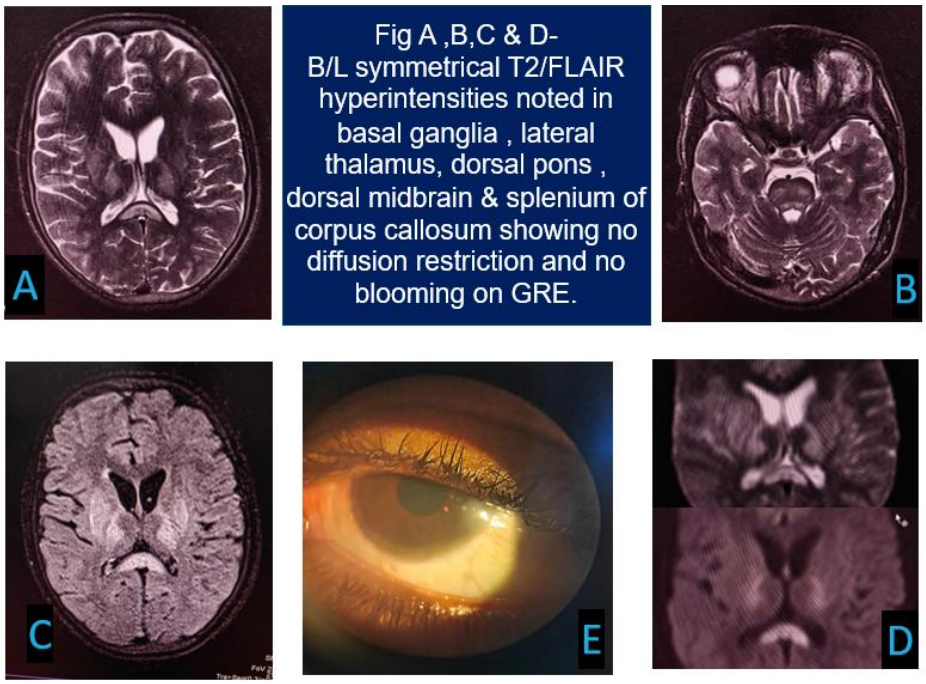

Figure 1: Axial T2/FLAIR MR images (A, B, D) show symmetric hyperintensity involving the basal ganglia, thalami, dorsal midbrain and dorsal pons; axial DWI (C) shows no diffusion restriction; slit-lamp photograph (E) demonstrates a Kayser–Fleischer ring at the corneal limbus.

A summary of the imaging findings and the sequences on which they were best appreciated is provided in Table 1.

Structure Involved	Signal Characteristics	Sequence Best Demonstrating Finding
Putamen and caudate nucleus (bilateral, symmetric)	T2/FLAIR hyperintensity (most characteristic)	T2W / FLAIR
Thalamus (medial/lateral)	T2/FLAIR hyperintensity	T2W / FLAIR
Midbrain (dorsal) / "face of the giant panda" region	T2/FLAIR hyperintensity with sparing of red nucleus and lateral pars reticulata	T2W / FLAIR (axial midbrain)
Pons (dorsal tegmentum)	T2/FLAIR hyperintensity	T2W / FLAIR
Splenium of corpus callosum	T2/FLAIR hyperintensity	T2W / FLAIR
Diffusion pattern	No significant diffusion restriction in the present case (chronic-stage pattern); restricted diffusion (↓ADC) may be seen in acute cytotoxic phase	DWI / ADC map
Susceptibility pattern	No blooming on GRE in the present case	GRE / SWI
Global parenchyma	Diffuse cerebral and cerebellar volume loss with ventricular dilatation	T1W / T2W

3. Discussion

The neurological manifestations of Wilson disease result from selective toxic accumulation of copper within the basal ganglia and brainstem. Excess free copper generates reactive oxygen species and induces mitochondrial dysfunction, oxidative injury, and astrocytic and neuronal damage, with the putamen and caudate nuclei affected earliest and most severely because of their high metabolic demand and relatively rich vascular supply.

On MRI, the most consistent and characteristic finding is bilateral, symmetric T2/FLAIR hyperintensity of the putamen, with variable involvement of the caudate nucleus, globus pallidus, thalamus, midbrain, pons, cerebellum and subcortical white matter, as seen in the present case. Involvement of the midbrain can produce the well-described

"face of the giant panda" sign – relative T2 hyperintensity of the tegmentum with preserved signal in the red nuclei and lateral portion of the pars reticulata of the substantia nigra, which appear as the panda's "eyes" – and, when pontine tegmental hyperintensity with sparing of the medial lemnisci and corticospinal tracts is also present, the "double panda sign." Hyperintensity of the splenium of the corpus callosum, as noted in this patient, has also been described and is thought to reflect either direct copper toxicity or Wallerian change secondary to adjacent thalamic injury.

Diffusion-weighted imaging provides additional information on disease activity. Restricted diffusion with low ADC values reflects cytotoxic oedema and is typically seen in the acute or subacute phase of neuronal injury, whereas increased ADC values in chronic disease reflect gliosis, demyelination and tissue loss. In the present case, the absence of diffusion restriction and susceptibility blooming on GRE suggested a more chronic, established stage of disease at the time of imaging, despite a relatively short symptomatic history, which may reflect a subclinical prodrome prior to overt presentation. Susceptibility-weighted or GRE sequences can occasionally show blooming related to paramagnetic copper or associated iron deposition, and their absence does not exclude the diagnosis.

Diffuse cerebral and cerebellar atrophy with ventricular dilatation, also seen in this patient, is a recognized accompaniment of longstanding neurological Wilson disease and correlates with disease duration and severity. A number of semi-quantitative MRI scoring systems, incorporating both acute white-matter signal abnormalities and chronic atrophic change, have been proposed to grade severity and to monitor response to de-coppering therapy, since imaging abnormalities and the associated clinical deficits may partially or completely reverse with early and adequate treatment.

The imaging differential diagnosis of symmetric basal ganglia and brainstem T2 hyperintensity in a young patient is summarized in Table 2 and includes Leigh disease, neurodegeneration with brain iron accumulation, hypoxic–ischemic encephalopathy, and osmotic demyelination syndrome. Distinguishing features in the present case – a strong family history, characteristic Kayser–Fleischer rings, and markedly reduced serum ceruloplasmin – allowed confident correlation of the imaging pattern with a diagnosis of Wilson disease. Slit-lamp confirmation of Kayser–Fleischer rings and biochemical assessment of ceruloplasmin (and, where available, 24-hour urinary copper excretion) therefore remain essential complements to imaging rather than substitutes for it.

Condition	Distinguishing Features
Leigh disease (subacute necrotizing encephalomyelopathy)	Onset in infancy/childhood; symmetric brainstem and basal ganglia lesions with cavitation; lactate peak on MR spectroscopy; normal ceruloplasmin and absent Kayser–Fleischer rings
Neurodegeneration with brain iron accumulation (NBIA)	T2 hypointensity from iron deposition (e.g., "eye-of-the-tiger" sign in PKAN) rather than the T2 hyperintensity typical of Wilson disease; normal copper/ceruloplasmin studies
Hypoxic–ischemic encephalopathy	Relevant history of hypoxic insult; predominant cortical and basal ganglia/thalamic involvement with acute diffusion restriction; no Kayser–Fleischer rings
Osmotic demyelination syndrome	History of rapid correction of hyponatremia; central pontine ± extrapontine hyperintensities with a characteristic trident/bat-wing pontine pattern; basal ganglia involvement less symmetric

Early recognition of this imaging pattern is of particular clinical importance because Wilson disease is one of the few neurodegenerative disorders of childhood and young adulthood that is both treatable and potentially reversible with timely institution of copper-chelating agents (such as D-penicillamine or trientine) or zinc therapy. Delay in diagnosis, as nearly occurred in this family given the earlier undiagnosed death of an elder sibling, can result in irreversible neurological disability or fulminant hepatic failure. This report is subject to the inherent limitations of a single-case description, including the absence of follow-up imaging after initiation of therapy, which would have allowed direct correlation between radiological and clinical improvement.

4. Conclusion

MRI is an essential and highly informative modality for detecting brain involvement in Wilson disease. Symmetric hyperintensities involving the basal ganglia, thalami, midbrain, pons and splenium of the corpus callosum on T2/FLAIR imaging represent the most important and consistent finding, while diffusion-weighted imaging assists in differentiating early cytotoxic injury from chronic gliotic change. Imaging findings should always be interpreted alongside clinical examination, slit-lamp assessment for Kayser–Fleischer rings, and serum ceruloplasmin levels. Prompt recognition of this constellation of findings enables timely treatment and meaningfully improves neurological outcome in an otherwise progressive but treatable disease.

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Conflict of Interest
None declared.

Source of Funding
Nil.

Ethical Considerations
Informed consent was obtained from the patient's guardian for publication of clinical details and images. Patient identity has been anonymized throughout.

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