https://doi.org/10.22516/25007440.1138

Case report

Wilson's Disease with Severe Neurological Presentation: A Case Report

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Citation:
Martínez-Montalvo CM, Niño-Gualdrón JL, Gómez-Zuleta MA. Wilson's Disease with Severe Neurological Presentation: A Case Report. Revista. colomb. Gastroenterol. 2024;39(4):465-471. https://doi.org/10.22516/25007440.1138

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Received: 10/09/2023
Accepted: 19/02/2024

Abstract

Introduction: Wilson's disease (WD) is an autosomal recessive disorder that can affect individuals of any age. Neurological involvement is reported in 30%–40% of patients, with dysarthria, ataxia, and dystonia being the primary manifestations. The presence of Kayser-Fleischer (KF) rings is observed in 77.2%–85.2% of cases. Chelation therapy demonstrates a paradoxical response in up to 50% of patients. We report a case of severe neurological presentation without KF rings, exhibiting a paradoxical response to chelation therapy. **Case Presentation:** A 23-year-old man with no prior medical history presented with a six-month history of symptoms consistent with vasovagal syncope episodes, followed by ataxia, muscle weakness, dysphagia, sialorrhea, and dysarthria. His condition progressively worsened due to sepsis of pulmonary origin secondary to an aspiration event. Investigations revealed low ceruloplasmin levels, elevated urinary copper, imaging findings consistent with thalamic and lenticular involvement, liver biopsy showing autoimmune hepatitis-like changes and features resembling non-alcoholic fatty liver disease (NAFLD), absence of KF rings, and a paradoxical response to chelation therapy. The disease course was marked by severe dystonia progression and a fatal outcome. **Conclusions:** WD is a condition with significant morbidity and a variable clinical spectrum. Isolated neurological involvement without KF rings is uncommon, and outcomes depend on early initiation of copper chelation therapy. However, paradoxical worsening of symptoms due to treatment, as observed in this case, poses an additional challenge.

Keywords

Wilson's disease, dystonia, penicillamine, copper.

INTRODUCTION

Wilson's disease (WD) is a rare condition with increasing prevalence[1,2]. It lacks a genotype-phenotype correlation and exhibits a wide spectrum of manifestations, affecting individuals aged 3 to 55 years. Neurological involvement is observed in 30% to 40% of cases and is associated with the presence of Kayser-Fleischer (KF) rings in 77.8% to 85.2% of cases[3], with similar findings reported in Colombian series (approximately 72.7%)[4]. Imaging findings in patients with neurological involvement are often non-specific, with the panda sign being the only late-stage pathognomonic finding[5]. Treatment primarily involves chelators, though the efficacy of combined therapy (chelators and zinc) remains debated due to high risks of side effects and paradoxical responses[3]. For severe neurological involvement, liver transplantation is still under discussion[6]. This report presents a clinical case of WD with less than one year of neurological manifestations, no chronic imaging findings, progression to severe dystonia, absence of KF rings, and a fatal outcome.

CASE DESCRIPTION

The patient was a 23-year-old male with no prior medical history, normal neurodevelopment, good academic per-

formance, and psychosocial functioning typical for his age. He reported no significant family medical history. Six months prior to his admission, he experienced a sudden two-minute loss of consciousness, with complete recovery, consistent with syncope. This event recurred four times in the following week, prompting multiple emergency department visits. Initial evaluations, including a positive tilt table test, supported a diagnosis of vasovagal syncope. Complementary studies, including echocardiography, carotid Doppler, non-contrast cranial CT, and 24-hour Holter monitoring, were normal.

Two months before admission, the patient developed progressive lower limb weakness, gait disturbances with an increased base of support, and incoordination of gross and fine motor activities. He also exhibited bradylalia, which progressed to mild dysarthria, dysphagia for solids and liquids, and sialorrhea. Subsequently, he experienced a tonic posturing episode involving flexion of the upper limbs, extension of the lower limbs, and retrocollis lasting one minute, with preserved consciousness and no sphincter relaxation or tongue biting. A non-contrast brain MRI revealed thalamic and lenticular nucleus lesions, hypointense on T1 and hyperintense on T2 and fluid-attenuated inversion recovery (FLAIR) sequences, with no additional abnormalities (**Figure 1**). Two electroencephalograms, one 6-hour and another 12-hour, showed no ictal activity. During clinical evolution, the patient displayed impaired attention (dysexecutive symptoms), recurrent overvalued anxious thoughts, and a labile and anxious mood, with intact memory, preserved sleep, and appetite.

The patient exhibited progressive deterioration characterized by episodes of tremors in the extremities, abnormal limb and neck posture, which became increasingly frequent and prolonged, ultimately impairing ambulation and resulting in immobility. Laboratory tests revealed mild normocytic normochromic anemia, elevated creatine phosphokinase (CPK), impaired renal function consistent with KDIGO stage II without chronic findings, and hepatic profile abnormalities with elevated transaminases, predominantly aspartate aminotransferase (AST) (**Table 1**). A repeat cranial CT scan was normal, as was a lumbar puncture with opening pressure and cerebrospinal fluid analysis. A bronchial aspiration episode led to sepsis of pulmonary origin, necessitating orotracheal intubation and prolonged invasive mechanical ventilation. Antibiotic therapy included piperacillin-tazobactam followed by meropenem.

Extended studies for Wilson's Disease (WD) revealed low ceruloplasmin, serum copper within normal limits, elevated urinary copper (766 µg/24 hours), and a liver biopsy performed due to persistent abnormal liver function tests. The biopsy showed moderate interface hepatitis, hepatocellular ballooning, and Mallory bodies (**Figure 2**). An ophthalmological evaluation found no evidence of Kayser-Fleischer (KF) rings, and imaging studies revealed no chan-

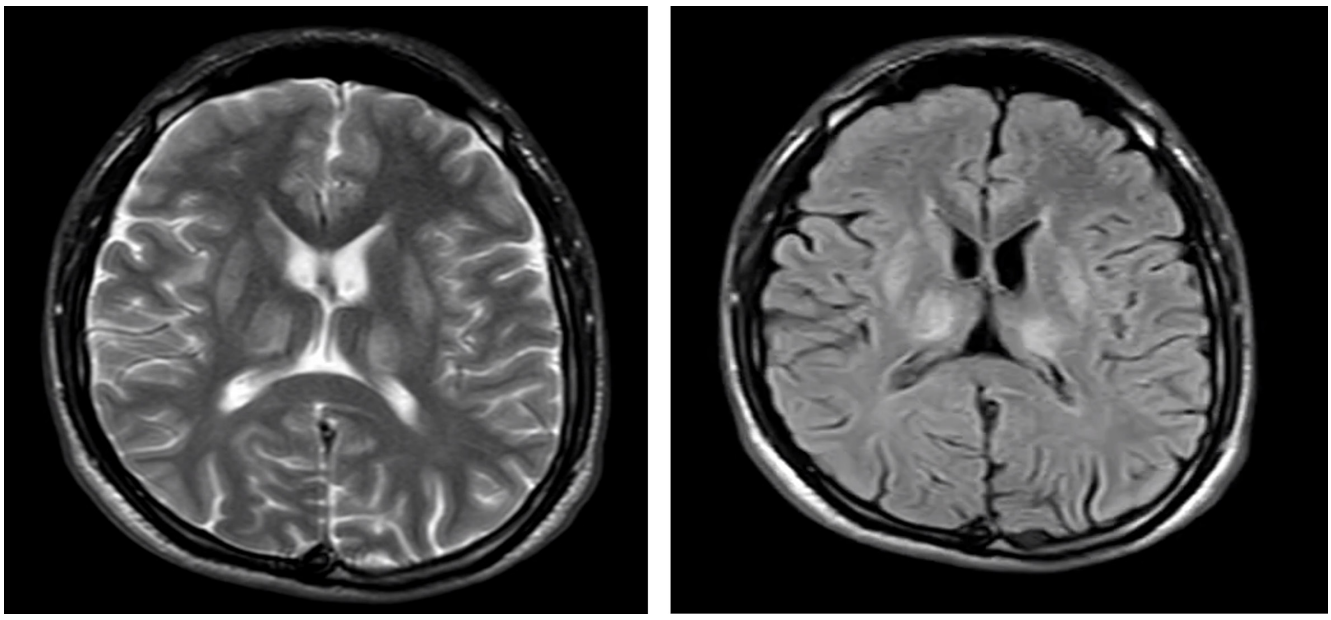

Figure 1. Brain MRI using T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences showing increased signal intensity in the basal ganglia, with greater involvement of the lentiform nucleus and thalamus bilaterally, without evidence of diffusion restriction. Source: Patient's medical records.

ges consistent with chronic liver disease. A Leipzig score of six points was calculated. Treatment included penicillamine at 15 mg/kg/day combined with zinc sulfate at 150 mg/day. Neurological deterioration occurred, marked by severe generalized dystonia predominantly affecting the oromandibular and cervical regions with pronounced retrocollis within three days of initiating chelation therapy (**Figure 3**). Intensive care unit (ICU) management involved cycles of neuromuscular relaxants combined with sedation using benzodiazepines (midazolam), baclofen, methadone, and gabapentin. Despite these interventions, clinical evolution was poor, leading to discussions with the family regarding the limitation of therapeutic efforts. The patient ultimately had a fatal outcome after four weeks of hospitalization.

This case documents WD presenting with severe neurological manifestations, secondary rhabdomyolysis, and the unique characteristic of absent ocular involvement, as no KF rings were detected. Additionally, the patient exhibited a paradoxical response to chelation therapy. This case adds to the literature with detailed observations and a review.

DISCUSSION

WD is an autosomal recessive disorder caused by mutations in the ATP7B gene on chromosome 13, with more than 700 mutations described. There is no established genotype-phenotype correlation, and epigenetic alterations play a significant role. The defect leads to impaired copper excretion, resulting in multi-organ damage due to tissue deposition[3].

Described in 1912 by Dr. Samuel Alexander Kinnier Wilson, its prevalence has increased to 30–142 cases per million[1,2]. Clinical manifestations are diverse, typically affecting adolescents or young adults, with an age range of 3 to 55 years. They include neurological involvement (30%–40%), hepatic involvement (30%–50%), psychiatric symptoms (30%–40%), and corneal KF rings[3,7].

This case presents unique features warranting analysis in the context of current knowledge. Notably, the absence of KF rings in a patient with neurological manifestations and cerebral imaging findings, despite disease onset less than a year prior, is unusual. In the literature, neurological symptoms vary widely; they are often mild or intermittent for years but can progress rapidly to severe deterioration within months. Damage predominantly affects the basal ganglia, with early symptoms including dysgraphia and gait and balance disturbances[1]. Manifestations range from involuntary movements to severe dystonia, with dysarthria being the most common symptom (46%–97%), followed by ataxia (28%–75%), dystonia (38%–69%), parkinsonism (12%–58%), and dysphagia (50%), among others[3]. There is no genotype-phenotype correlation for neurological manifestations in WD[3,8], and MRI findings do not consistently align with clinical presentation or treatment response[3].

Some significant findings indicate that up to 83.3% of patients with neurological manifestations of Wilson's Disease (WD) have documented hepatic involvement, with hepatic copper content measured by spectroscopy exceeding 250 µg/g of liver dry weight[3]. Although local

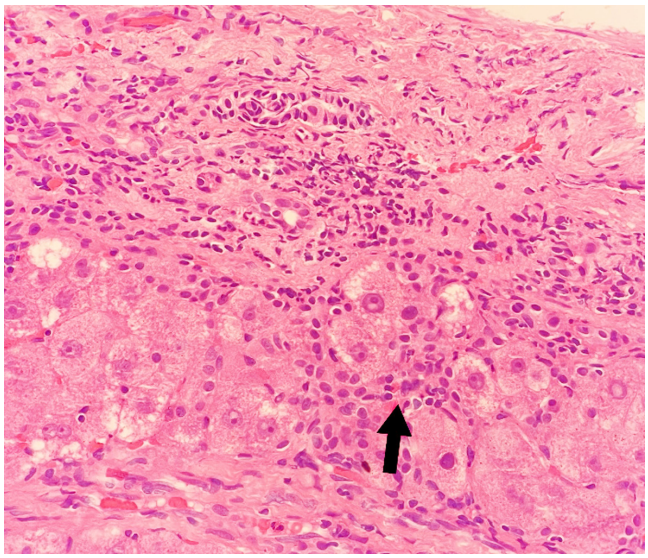

Figure 2. Liver Biopsy stained with hematoxylin and eosin, showing lymphoplasmacytic infiltrate with evidence of limiting plate destruction. Source: Patient's medical records.

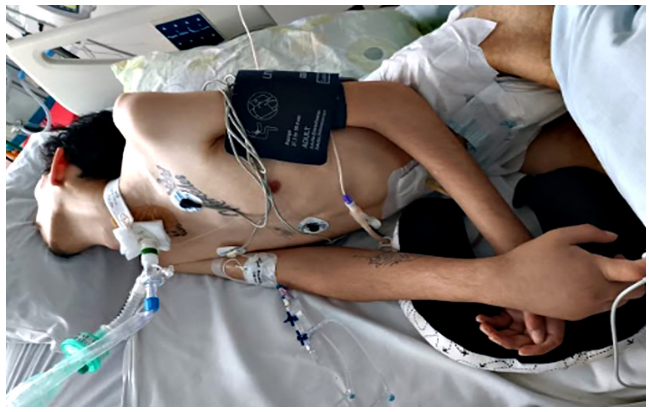

Figure 3. Severe Dystonia with Pronounced Retrocollis. Source: Patient's medical records.

Table 1. Laboratory Results

Laboratory Test	Reference Range	Resultados
White blood cells (×10³/µL)	5.1-9.7	10.19
Differential Count (%)		
Neutrophils	39.6-64.6	85.9
Lymphocytes	20.7-39.6	9
Monocytes	1-12.6	3.5
Eosinophils	1-3.9	0.4
Basophils	0.01-1	0.1
Absolute Counts ×10³/µL)		
Neutrophils	1.4-6.5	8.76
Lymphocytes	1.2-3.4	0.91
Monocytes	0-0.7	0.36
Eosinophils	0-0.7	0.04
Basophils	0-0.2	0.01
Red blood cell count (×10⁶/µL)	4.5-5.5	3.77
Hemoglobin (g/dL)	14-18	11.5
Hematocrit (%)	42-56	34.2
Mean corpuscular volume (fL)	80-100	90.7
Mean corpuscular hemoglobin (pg)	27-34	30.5
Mean corpuscular hemoglobin concentration (g/dL)	31.5-35	33.6
Red cell distribution width (%)	November 15	12.9
Platelet count (×10³/µL)	150-450	145
Platelet volume (fL)	6.4-13	10
C-reactive protein (mg/L)	0-3	84
Creatinine (mg/dL)	0.67-1.17	0.54
Blood urea nitrogen (mg/dL)	July 18	15.22
Sodium (mmol/L)	135-145	143.42
Potassium (mmol/L)	3.5-5	3.29
Chloride (mmol/L)	98-107	108.84
Calcium (mg/dL)	8.5-10.1	7.75
Magnesium (mg/dL)	1.8-2-4	2.1

Laboratory Test	Reference Range	Result
Total creatine kinase (U/L)	39-308	5836
Vitamin B12 (pg/mL)	211-911	808
Total bilirubin (mg/dL)	0.2-1	0.72
Direct bilirubin (mg/dL)	0-0.2	0.23
Indirect bilirubin (mg/dL)	0-1.1	0.49
Alkaline phosphatase (UL)	58-237	107.4
Aspartate aminotransferase (U/L)	15-37	131.87
Alanine aminotransferase (U/L)	16-63	146.23
γ-glutamyl-transferase (U/L)	0-55	181.33
Prothrombin time (seconds)	11.8-16.1	13.3
International normalized ratio (seconds)	0.5-1.5	1.14
Partial thromboplastin time (seconds)	24.3-35	33.8
Serum albumin (g/dL)	3.8-4.4	2.5
Lactate dehydrogenase (U/L)	85-227	391.2
Storage Disease Screening		
- Serum copper (µg/dL)	70-140	<25
- 24-hour urine copper (µg/24h)	<60	766.53
- Ceruloplasmin (mg/dL)	20-60	5.0
- Total serum iron (µg/dL)	65-175	31.7
- Ferritin (ng/mL)	20-99	540.79
- Transferrin saturation (%)	20-50	20.98
- Iron-binding capacity (µg/dL)	250-450	151
Lipid Profile		
- Total cholesterol (mg/dL)	0-200	132.13
- High-density lipoprotein (mg/dL)	40-60	25.01
- Triglycerides (mg/dL)	<150	120.9
- Thyroid-stimulating hormone (µIU/mL)	0.55-4.78	2.98

Source: Patient's medical records.

data are limited, neurological involvement has been observed in 40% of WD patients, with parkinsonism (14%) and dystonia (11%) being the most common manifestations. Among patients with WD and documented neurological involvement, none had detectable copper deposits in liver biopsies, 72.7% exhibited Kayser-Fleischer (KF) rings, 81% had low ceruloplasmin levels, and elevated urinary copper was observed in only 54.5% of cases[4].

What makes our patient's case unusual is the absence of KF rings or sunflower cataracts. Neurological manifestations of WD without ocular involvement are rare in the literature. It has been reported that KF rings are present in 77.8%–85.2% of patients with neurological or psychiatric involvement[7,9], in 36%–62% of patients with hepatic manifestations, and in 10%–30% of asymptomatic patients[9]. Local data show that only 40% of all newly diagnosed WD cases and 72.7% of cases with neurological involvement had KF rings identified by slit-lamp exam[4]. In this case, no ocular involvement was documented, but hepatic involvement was present. This initially necessitated the exclusion of other differential diagnoses due to the atypical presentation. Optical coherence tomography of the anterior segment could have been a useful alternative to rule out ocular involvement, given the slit-lamp's sensitivity of approximately 50%[9].

The diagnosis of WD also includes evidence of hepatopathy, and abdominal ultrasonography can aid in identifying the disease. Depending on the stage of WD, abdominal ultrasound may reveal hepatomegaly or signs of chronic liver disease[10]. Liver biopsy remains essential for quantifying hepatic copper, assessing the degree of inflammation and fibrosis, ruling out other diseases, and potentially evaluating treatment response[11]. Histological findings in WD include autoimmune-like hepatitis, fibrosis, fatty infiltration, cirrhosis, hepatocellular ballooning, and Mallory-Denk bodies, among others. However, these findings are non-specific. In analyzing hepatic copper, it is important to consider its heterogeneous deposition in the liver, varying by lobe in early stages and by nodule in cirrhosis. This variability can lead to negative staining results, making such tests less sensitive, and a negative result does not exclude the diagnosis. A more reliable test is the measurement of hepatic copper concentration, where levels <50 μg/g of liver dry weight are normal, and levels >250 μg/g indicate abnormal copper deposition[3,12]. In the presented case, there were no imaging findings indicative of cirrhosis, but moderate chronic hepatitis and autoimmune-like hepatitis were observed. These findings bear similarities to changes seen in nonalcoholic fatty liver disease (NAFLD).

In magnetic resonance imaging (MRI), early abnormalities are often non-specific but can be valuable for diagnosing unexplained neurological or psychiatric symptoms. Findings may include alterations in the basal ganglia, thalami, pons, and white matter. Data show evidence of cerebral atrophy, bilateral symmetrical lesions in the caudate and putamen (characterized by concentric laminar increases in T2 signal intensity), and T2 signal hyperintensities in the substantia nigra (pars compacta), periaqueductal gray matter, pontine tegmentum, and thalamus. Additionally, T2 signal hyperintensities may be observed in the periaqueductal gray matter, substantia nigra, and around the red nuclei, which maintain their normal hypointensity. A late-stage hallmark, the panda sign, consists of T2 hyperintensity in the midbrain and has been considered pathognomonic. However, similar changes may be seen in chronic liver disease, which must be taken into account. It is clear that MRI is not useful for determining prognosis or monitoring neurological symptoms[3,5]. In the present case, the disease onset was less than 12 months, and hyperintensity in the basal ganglia was documented without evidence of the panda sign, suggesting a rapidly progressive course driven by neurological involvement.

Adverse effects at the initiation of therapy remain a major concern, particularly due to the risk of neurological deterioration after starting any of the three main medications. This occurs most frequently with penicillamine (13.8%), followed by trientine (8%) and zinc (4.3%)[13]. Neurological deterioration has been reported in up to 50% of patients initiating penicillamine, and as many as 30% of patients may discontinue therapy due to adverse events, making this drug one that requires special caution. Although most guidelines recommend starting treatment with penicillamine, recent data from a clinical trial (the Chelate trial) with 48 weeks of follow-up demonstrated that trientine tetrahydrochloride is not inferior to penicillamine and is comparable in terms of side effects[14].

There is currently no clear evidence on whether combination therapy with chelators and zinc offers advantages over monotherapy, nor are there comparative data on its safety profile. The decision to initiate combination therapy is primarily based on clinical judgment and the mechanism of action rather than efficacy or safety[3]. Another therapy under evaluation is bis-choline tetrathiomolybdate (ALXN840), which acts by forming a tripartite complex with copper and albumin, followed by biliary excretion. Preclinical and phase III studies have shown that in ATPB7(-) mice, this therapy is not inferior to D-penicillamine or trientine in reducing hepatic copper levels. However, high doses have been associated with potential mitochondrial damage. Results from ongoing studies are still awaited[15]. Additionally, methanobactin therapy in animal studies has demonstrated strong cop-

per-binding affinity and promising results in preventing copper-induced mitochondrial damage and improving histological outcomes. In terms of precision medicine, adeno-associated virus vectors encoding human ATP7B complementary DNA (cDNA) in hepatocytes of a WD mouse model have demonstrated effective ATP7B expression and reduction in hepatic copper levels. Shorter vectors have also shown long-term normalization of copper levels in mice. Furthermore, liver cell transplantation therapies have reduced fulminant hepatitis, decreased inflammation, and improved short-term survival[8].

In this case, combination therapy with zinc and penicillamine was initiated, primarily based on clinical judgment regarding the disease's progression and resource availability. However, neurological deterioration was subsequently documented, raising concerns about the optimal therapy for neurological forms of WD.

In the multidisciplinary management approach, the possibility of liver transplantation was considered based on very limited data, primarily from small cohorts in France and Italy. However, clinical outcomes remain unclear, and severe neurological involvement is still not an established indication for liver transplantation[6].

CONCLUSION

WD is a disease with significant morbidity and a wide spectrum of clinical manifestations. Neurological presentations without KF rings are uncommon. The prognosis of neurological manifestations depends heavily on the early initiation of copper-chelating therapy, despite the risk of neurological deterioration associated with treatment initiation. Liver transplantation for severe neurological manifestations remains a controversial topic.

Ethical Approval and Participant Consent

This report was approved by the patient and their family.

Consent for Publication

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Data and Material Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Conflict of Interest

The authors declared no conflicts of interest.

Funding Sources

The authors received no financial support.

Author Contributions

All authors analyzed and interpreted the patient data, wrote the manuscript, reviewed and interpreted the imaging, and contributed to manuscript preparation. All authors read and approved the final manuscript.

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Enfermedad de Wilson con una presentación neurológica grave: reporte de caso

Revista colombiana de Gastroenterología
vol. 39, no. 4, p. 465 - 471, 2024
Asociación Colombiana de Gastroenterología,
ISSN: 0120-9957
ISSN-E: 2500-7440

DOI: https://doi.org/10.22516/25007440.1138