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By Laryssa Garcia de Almeida, Ilana Werneck Augsten, Yan da Silva Raposo, Hiago Antunis Silva, Patrícia Marques Mendes, Igor Pereira Matos de Oliveira & Eduardo Mendonça Werneck da Silva

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NEUROLOGICAL WILSON DISEASE IN A YOUNG BRAZILIAN ADULT CASE REPORT

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Neurological Wilson Disease in a Young Brazilian Adult: A Case Report

Laryssa Garcia de Almeida ^α, Ilana Werneck Augsten ^σ, Yan da Silva Raposo ^ρ, Hiago Antunis Silva ^ω, Patrícia Marques Mendes [¥], Igor Pereira Matos de Oliveira [§] & Eduardo Mendonça Werneck da Silva ^χ

Abstract- We report a rare case of Wilson's Disease with neurologic features in a 31-year-old man. This disease consists of a disturbance of copper metabolism secondary to a mutation in the gene responsible for encoding the tissue transporter and the enzyme that incorporates the excess element into bile, generating toxic accumulation in the liver, cornea, and central nervous system. According to his wife, the patient had been treated for an unspecified mood disorder. The clinical picture was characterized by depressive mood, anhedonia, and anxiety. He had his first seizure episode on December 3rd, 2021. He progressed with dysarthria, ataxic gait, dystonia of the right-hand flexor muscles, and intermittent urinary incontinence. Marked worsening was observed after the diagnosis of COVID-19 in February 2022. At the clinical evaluation on March 24th, risorius muscle dystonia (risus sardonicus), resting tremor, and Kayser Fleischer rings at slit-lamp examination was also noted. Cerebrospinal fluid exam without abnormalities. Imaging workup revealed signaled alteration in bilateral putamen, midbrain, and pons. Laboratory tests revealed mild impairment of liver function and abdominal ultrasound with no evident abnormalities. Specific tests confirmed the diagnosis (serum copper and 24-hour urine copper levels elevated and reduced serum ceruloplasmin). This case report represents the importance of a detailed neurological clinical evaluation and the association of findings with imaging and laboratory workup. It is a rare disease whose epidemiology in Brazil lacks data, and complementary tests have reduced specificity. Early diagnosis and treatment have an impact on the neurological prognosis.

Keywords: wilson disease. inborn errors in metal metabolism. dystonia.

I. INTRODUCTION

Wilson's Disease (WD) is a metabolic disorder resulting from biallelic mutations in the ATP7B gene on chromosome 13^{1,2,3} of autosomal recessive inheritance³, characterized by the toxic accumulation of this element in the liver, cornea, and central nervous system⁴.

Author α ω: Neurology Specialist, Hospital das Clínicas Samuel Libânio, 777 Comendador Jose Garcia St, Pouso Alegre, Minas Gerais, MG 37550-000, BRA.

Author σ: Neurology Specialist, Fellowship in Vascular Neurology, Hospital das Clínicas Samuel Libânio, 777 Comendador Jose Garcia St, Pouso Alegre, Minas Gerais, MG, 37550-000, BRA.

Author ρ ¥ § χ: Neurology Resident, Hospital das Clínicas Samuel Libânio, 777 Comendador Jose Garcia St, Pouso Alegre, Minas Gerais, MG, 37550-000, BRA. e-mail: yanraposo@yahoo.com.br

The incidence of these mutations in newborns was estimated at 1:7,000 in Sardinia, Italy⁵ and 1.7:100,000 in the Republic of Ireland⁶, in contrast, the prevalence of the disease has been estimated to be between 1:250,000 and 1:300,000 in Sweden and between 1:30,000 and 1:40,000 in other populations⁷.

Copper is an essential cofactor for several enzymes⁸ and is present in foodstuffs such as seafood, pulses, and nuts⁹. Its metabolism is dependent on the ATP7B gene, which is responsible for encoding ceruloplasmin, and on the ATPase, which incorporates it into the bile and allows its exteriorization with the feces^{10,11}.

Due to the absence of these mechanisms, copper accumulates in the liver until it spills over into the bloodstream. High levels of cupremia cause disruption of the blood-brain barrier and deposition with a cytotoxic effect in the striatum, globus pallidus, locus coeruleus, substantia nigra, and cerebral cortex^{4,12}.

II. CASE REPORT

A 31-year-old male, mixed race, bricklayer, residing in Paraisópolis, Minas Gerais State, Brazil. History of alcoholism and drug use. Diagnosis of previous unspecified mood disorder and using Fluoxetine 40mg/day. No other relevant environmental exposures were reported. Report of a male adult family member diagnosed with liver failure of unknown etiology.

Magnetic Resonance Imaging (MRI) of the brain on December 1st, 2021, showed involvement of the putamen, associated with hemosiderin residue, and crus posterius bilaterally, in addition to the midbrain and pons, without restriction to diffusion (images 1A-1D), and an extra-axial parietal left paramedian contrast-enhanced lesion suggestive of meningioma (images 1E-1F). On December 3rd, 2021, the patient suffered the first generalized clonic tonic seizure while sleeping, and in a follow-up visit on December 21st, he started to use Levetiracetam orally.

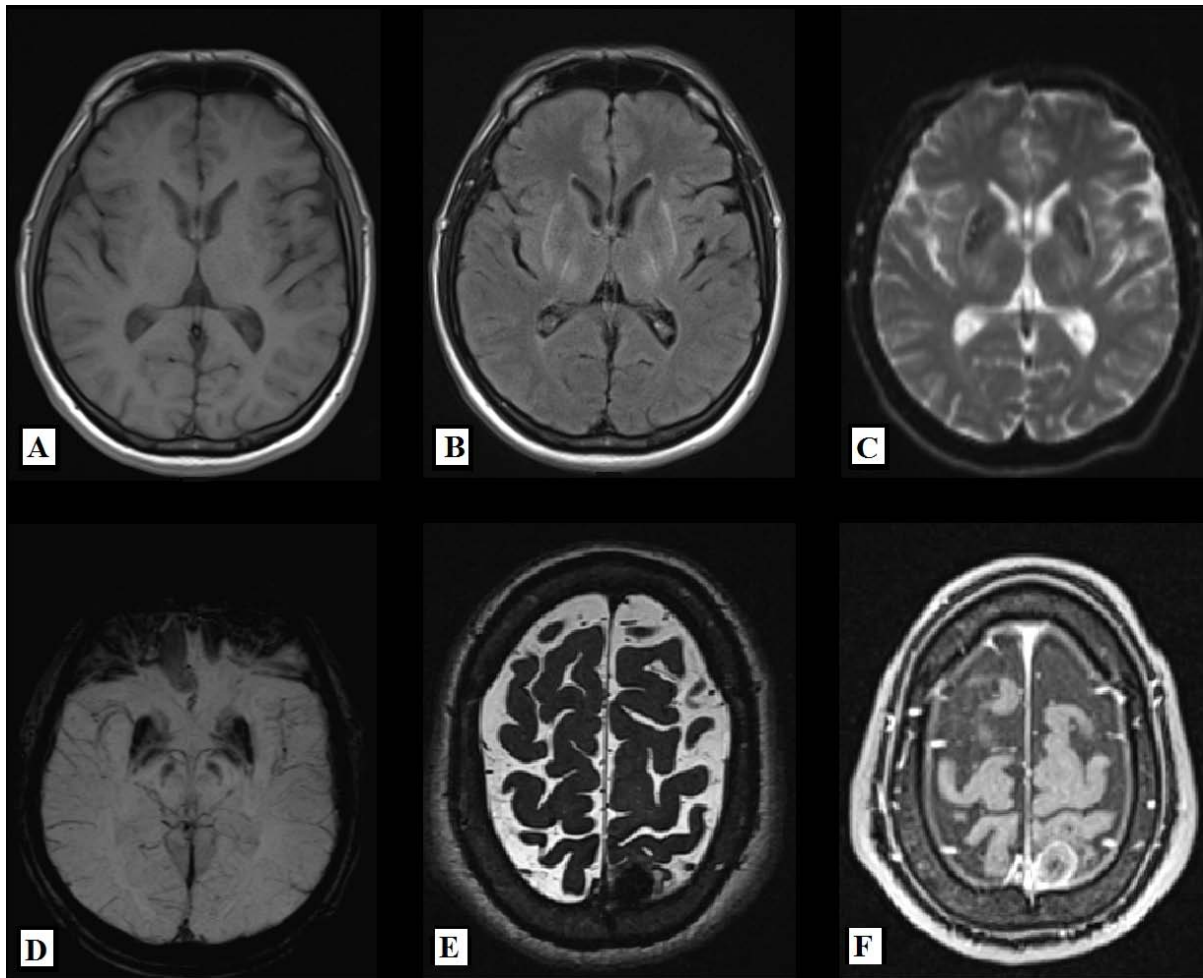
He was diagnosed with Covid 19 on February 3rd, 2022, with a mild evolution without the need for ventilatory support or complications. The wife noted that the development of the disease was accentuated after the infection. From February 9th, he appeared to have speech and gait disturbance, difficulty mobilizing the right hand, and urinary incontinence.

On February 16th, he attended the consultation with the responsible physician who, associated the symptoms with the anticonvulsant and switched to Phenytoin 100mg twice a day and associated Dexamethasone orally. It evolved five days later with intermittent hiccups and prostration that lasted approximately three days.

Cerebrospinal fluid (CSF) collected On March 21st revealed a cell count of 0 unit; glucose 89 mg/dL,

lactate 15.7 mg/dL, gram without staining bacteria, and CSF culture without bacterial growth.

He was hospitalized on March 24th for social reasons to collect WD screening tests. The patient presented to the neurological examination with regular general condition, good spatial orientation, alertness, Glasgow Coma Scale 15, hypomimia, cranial nerve pairs exam without abnormalities, isochoric pupils, normal extrinsic ocular

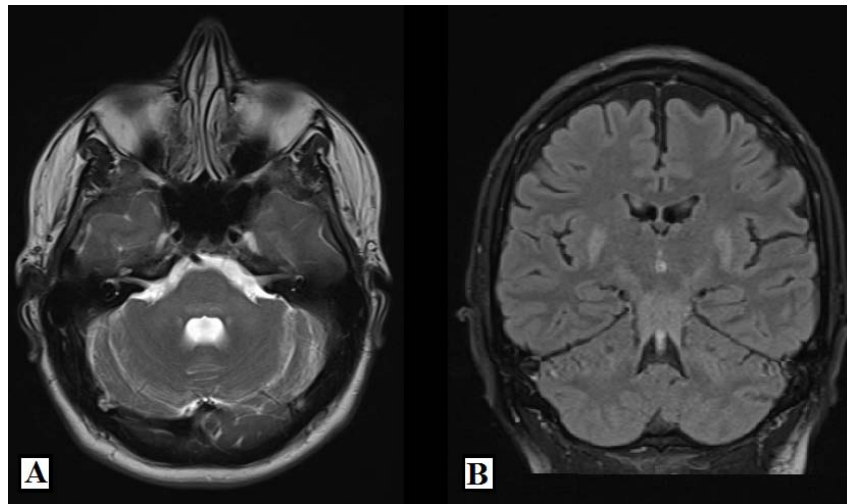


motricity, risus sardonicus, deep tendon reflexes 2/2, muscle strength 5/5 in all testable upper and lower limb muscle groups, somaesthesia, right-hand flexor dystonia, and ataxic gait. Upon slit lamp examination, the presence of Kayser-Fleischer rings was noted.

Laboratory workup of March 24th revealed aminotransferase (AST) 37 mg/dL, alanine aminotransferase (ALT) 35 mg/dL, total bilirubin test 1,00 mg/dL, albumin test 3,7 mg/dL, international normalized ratio (INR) 1,17, and platelets 88×10^9 /L. Tests for disorders of Copper metabolism of the same date revealed total serum copper 24,6 mg/dL (reference range (RR) 70mg/dL-150mg/dL), serum ceruloplasmin 7,0 mg/dL (RR 20mg/dL-60mg/dL) and, finally, 24-hours urine copper test 187,4 mg/dL (RR 70mg/dL-150mg/dL). Child-Pugh, Fibrosis-4, and APRI scores were, respectively, 5 points (Child Class A - least severe

liver disease); 1,99 (undetermined), and 1,11 (significant fibrosis most likely, cirrhosis undetermined). Abdominal ultrasound exam of April 8th, 2022, indicates chronic liver disease with signs of portal hypertension, splenomegaly, and moderate ascites. Electroneuromyography of March 14th, 2022, was absent abnormalities.

During outpatient follow-up, a new MRI of the brain was requested on April 1st, 2022, which denoted better characterization of foci of signal alteration in cerebellar peduncles (images 2).



On June 2022, he had moderate dysarthria, hypomimia, right-hand flexor dystonia, tetraparesis, bradykinesia, and postural instability, but without rigid or resting tremors.

The specific treatment was started on May 2022 with pyridoxine chlorhydrate 50 mg daily and zinc sulfate heptahydrate 4 mg/mL 15mL three times a day orally. Due to the cost of the drug, the patient delayed starting penicillamine.

III. DISCUSSION

Incipient neurological symptoms are subtle and nonspecific, such as difficulty concentrating and motor coordination and handwriting changes (for example, micrograph) ¹³⁻¹⁹ and begin on average between 20 and 40 years ²⁰⁻²². As it progresses, more prominent symptoms appear, whose order of incidence is dysarthria (57.6%), dystonia (42.4%), abnormal gait (37.8%), tremor (36.2%), parkinsonism (17.3%), choreoathetosis (15.3%) and convulsion (4.7%) ^{16,17}. Neurological impairment occurs about a decade after liver failure and, therefore, signs of advanced disease ²³. Cognitive impairment is considered rare and was reported by Machado, Chien, Deguti, et al. (2006) ¹⁶ in 4.2% of cases.

Given the heterogeneity of clinical manifestations, the neurological phenotype of WD can be grouped for didactic purposes into dystonic, pseudosclerotic, parkinsonian, and hyperkinetic subtypes ⁴. The patient discussed in this study had a predominance of the dystonic subtype manifested by multifocal dystonia affecting both the risorius muscle (sardonic laughter) and the flexor muscles of the right hand fingers. As reported by Lorincz (2010) ²⁴, bilateral putaminal lesions were found on an MRI of the brain.

Dysarthria can result from any condition that damages the motor control structures necessary for speech production, such as cranial nerves IX, X, XII, cerebellum, and basal ganglia ¹². In this case, it was noted evident bilateral impairment of the basal ganglia.

Seizures are not uncommon and are reported variably in 4.7% ^{16,17} to 14.5% ²⁵ of WD cases. The patient in question presented, at the initial manifestation, a single episode of generalized tonic-clonic seizure without recurrence.

We also detected the presence of brownish Kayser Fleischer rings, more evident in the lower region of the iris bilaterally. Such a semiological sign is due to copper deposition in the Descemet's membrane of the cornea ²⁶ and is present in approximately 100% of neuropsychiatric WD cases ¹⁰.

Psychiatric symptoms are reported by about 30% to 60% of individuals affected by WD ²⁶. In this case, the disorder for which the patient had been using Fluoxetine was not specified. However, the familiar states that at the time of initiation of therapy, he had a depressive mood, anhedonia, and anxiety.

It is possible that such symptoms were already an incipient manifestation of central nervous system involvement.

Cognitive impairment is initially mild and recognized only by family members. It is categorized into frontal lobe syndrome, which involves impulsivity, promiscuity, apathy, hypotenacity, impaired social judgment, planning dysfunction, and emotional lability, and subcortical dementia characterized by slowed thinking amnesia, and executive dysfunction, but without aphasia, apraxia, or agnosia ¹⁰. In this case, it was impossible to attribute a clinical syndrome related to the metabolic disorder, given the history of alcoholism and use of narcotics.

IV. CONCLUSION

This case report represents the importance of a detailed neurological clinical evaluation and the association of findings with Imaging and laboratory workup. It is a rare disease whose epidemiology in Brazil lacks data, and complementary tests have reduced specificity.

Disclosure statement

No potential conflict of interest was reported by the authors.

REFERENCES RÉFÉRENCES REFERENCIAS

1. Bull PC, Tomás GR, Rommens JM, Forbes JR, Cox DW. The Wilson disease gene is a putative copper transporting P-type ATPase similar to the Menkes gene. *Nat. Genet.* 1993; 5: 327-337.
2. Tanzi RE, Petrukhin K, Chernov E, Pellequer JL, Wasco W, Ross B, et al. The Wilson disease gene is a copper transporting ATPase with homology to the Menkes disease gene. *Nat. Genet.* 1993; 5: 344-350.
3. Faucher M, Caroline D. The psychopharmacology of Wilson disease and other metabolic disorders. *Handbook of clinical neurology.* 2019; 165: 191-205.
4. Hedera P. Wilson's disease: A master of disguise. *Parkinsonism & Related Disorders.* 2019; 59: 140-145.
5. Loudianos G, Dessi V, Lovicu M, Angius A, Figus A, Lilliu F, et al., Molecular characterization of Wilson disease in the Sardinian population—evidence of a founder effect. *Hum. Mutat.* 1999; 14: 294-303.
6. Reilly M, Daly L, Hutchinson M. An epidemiological study of Wilson's disease in the Republic of Ireland. *Journal of Neurology, Neurosurgery & Psychiatry.* 1993; 56(3): 298-300.
7. Olsson C, Waldenström E, Westermark K, Landegre U, Syvanen AC. Determination of the frequencies of ten allelic variants of the Wilson disease gene (ATP7B), in pooled DNA samples. *Eur. J. Hum. Genet.* 2000; 8: 933-938.
8. Lopes LAL, Souza SEM, Filho VMA, Borges MAF. Mielopathy related to copper deficiency after bariatric surgery: case report Mielopatia relacionada à deficiência de cobre após cirurgia bariátrica: relato de caso. *Brazilian Journal of Health Review.* 2021; 4(6): 27188-94.
9. Roberts EA, Schilsky ML. American association for study of liver diseases (AASLD). Diagnosis and treatment of Wilson's disease: an update. *Hepatology.* 2008; 47: 2089-2111.
10. Lorincz MT. Wilson disease and related copper disorders. *Handbook of Clinical Neurology.* 2018; 147: 279-292.
11. Tussolini IGA, Tussolini GR, Tussolini JF, Pontes LS, Junior MTR, Silva, PD. Doença de Menkes: relato de um caso raro na Amazônia. *Brazilian Journal of Health Review.* 2023; 6(1): 4016-26.
12. Ortiz JF, Cox AM, Tambo W, Eskander N, Wirth M, Valdez M, et al. Neurological Manifestations of Wilson's Disease: Pathophysiology and Localization of Each Component. *Cureus.* 2020; 12(11):e11509.
13. Walshe JM. Wilson's disease. The presenting symptoms. *Arch. Dis. Child.* 1962; 37: 253-256.
14. Saito T. Presenting symptoms and natural history of Wilson disease. *Eur. J. Pediatr.* 1987; 146: 261-265.
15. Oder W, Grimm G, Kollegger H, Ferenci P, Schneider B, Deecke L. Neurological and neuropsychiatric spectrum of Wilson's disease: a prospective study of 45 cases. *J. Neurol.* 1991; 238: 281-287.
16. Machado A, Chien HF, Deguti MM, Cançado E, Azevedo RS, Scaff M, et al. Neurological manifestations in Wilson's disease: report of 119 cases. *Mov. Disord.* 2006; 21: 2192-2196.
17. Burke JF, Dayalu P, Nan B, Askari F, Brewer GJ, Lorincz MT. Prognostic significance of neurologic examination findings in Wilson disease. *Park. Relat. Disord.* 2011; 17: 551-556.
18. Członkowska A, Litwin T, Dzieżyc K, Karliński M, Bring J, Bjartmar C. Characteristics of a newly diagnosed Polish cohort of patients with neurological manifestations of Wilson disease evaluated with the Unified Wilson's Disease Rating Scale. *BMC Neurol.* 2018; 18: 34.
19. Rubinstein SS, Young AB, Kluin K, Hill G, Aisen AM, Gabrielsen T, et al. Clinical assessment of 31 patients with Wilson's disease. Correlations with structural changes on magnetic resonance imaging. *Arch. Neurol.* 1987; 44: 365-370.
20. Cauza E, Dobersberger TM, Polli C, Kaserer K, Kramer L, Ferenci P. Screening for Wilson's disease in patients with liver diseases by serum ceruloplasmin. *J. Hepatol.* 1997; 27: 358-362.
21. Xu X, Pin S, Gathinji M, Fuchs R, Harris ZL. Aceruloplasminemia: an inherited neurodegenerative disease with impairment of iron homeostasis. *Ann. N. Y. Acad. Sci.* 2004; 1012: 299-305.
22. Tümer Z. An overview and update of ATP7A mutations leading to Menkes disease and occipital horn syndrome. *Hum. Mutat.* 2013; 34: 417-429.
23. Ferenci P. Pathophysiology and clinical features of Wilson disease. *Metabolic brain disease.* 2004; 19: 229-39.
24. Lorincz MT. Neurologic Wilson's disease. *Ann N Y Acad Sci;* 2010; 1184: 173-187.
25. Prashanth LK, Sinha S, Taly AB, Mahadevan A, Vasudev MK, Shankar SK. Spectrum of epilepsy in Wilson's disease with electroencephalographic, MR imaging and pathological correlates. *J Neurol Sci.* 2010; 291: 44-51.
26. Stremmel W, Merle U, Weiskirchen R. Clinical features of Wilson disease. *Annals of Translational Medicine.* 2019; 7(2): 61.