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Neurological Wilson's disease

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ABSTRACT
We describe the clinical aspects of Wilson's Disease with neurologic features. 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. Incipient neurological symptoms are subtle and nonspecific, such as difficulty concentrating, coordination, and handwriting changes (for example, micrograph), and begin on average between 20 and 40 years. Laboratory tests reveal impairment of liver function. Specific tests confirm the diagnosis (serum copper and 24-hour urine copper levels elevated and reduced serum ceruloplasmin). Imaging workup can reveal signaled alteration in striatum, and bilateral putamen, midbrain, and pons. 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 metal metabolism, Dystonia.

1 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 inheritance[3], characterized by the toxic accumulation of this element in the liver, cornea, and central nervous system[4].

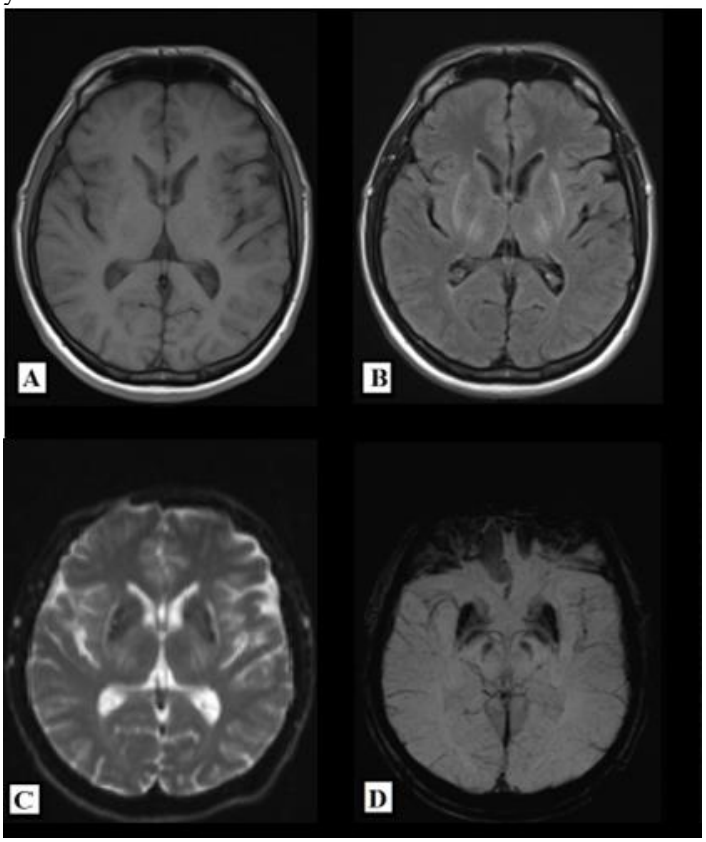
Copper is an essential cofactor for several enzymes[5] and is present in foodstuffs such as seafood, pulses, and nuts[6]. Its metabolism is dependent on the ATP7B gene, which is responsible for encoding ceruloplasmin, and on the ATPase, which incorporates it into the bile and allows its exteriorization with the feces [7,8].

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 [4,9] (images 1 and 2).

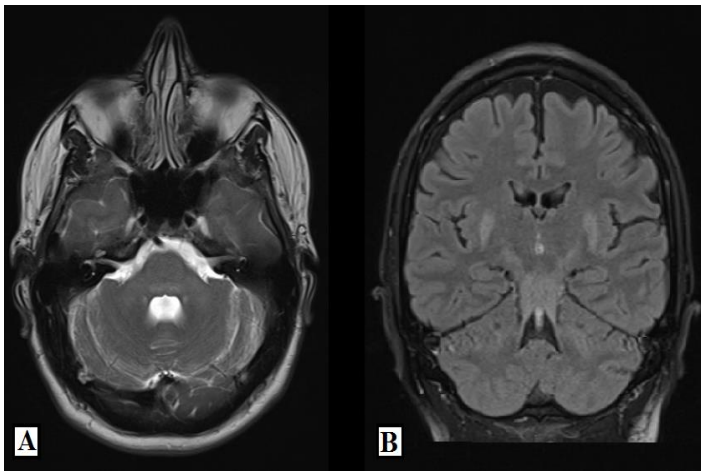
2 EPIDEMIOLOGY

The incidence of these mutations in newborns was estimated at 1:7,000 in Sardinia, Italy[10] and 1.7:100,000 in the Republic of Ireland[11], 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 populations[12] .

Images 1– Brain MRI. (A)T1 weighted imaging (T1WI) without abnormalities. (B) T2-weighted-Fluid-Attenuated Inversion Recovery (T2/FLAIR) imaging exhibited a hyperintense signal in putamen and crus posterius bilaterally. (C) T2WI exhibited a hyposignal in striatum. (D) Susceptibility-weighted imaging (SWI) showed a hyposignal in basal ganglia. Source: courtesy of Mrs Laryssa Garcia de Almeida.



Images 2 – Brain MRI. T2WI (A) and T2/FLAIR imaging (B) showed better foci of signal alteration in cerebellar peduncles.



Source: courtesy of Mrs Laryssa Garcia de Almeida

3 SIGN AND SYMPTOMS

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].

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[9].

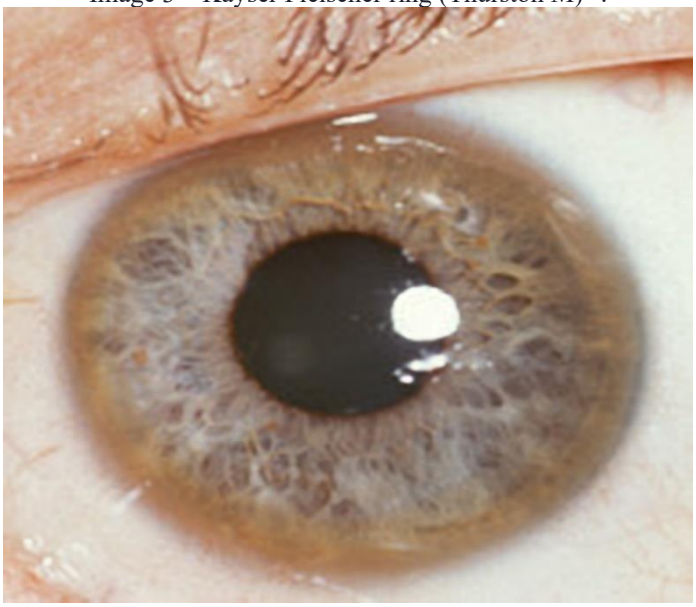
Seizures are not uncommon and are reported variably in 4.7% [16,17] to 14.5%[23] of WD cases.

Kayser Fleischer rings is due to copper deposition in the Descemet's membrane of the cornea[25] and is present in approximately 100% of neuropsychiatric WD cases [7] (image 3).

Psychiatric symptoms are reported by about 30% to 60% of individuals affected by WD[25].

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[7].

Image 3 – Kayser Fleischer ring (Thurston M)[26].



4 DIAGNOSIS

Screening tests are recommended as the first step in diagnosing Wilson's Disease, such as ophthalmologic slit-lamp examination for Kayser-Fleischer rings, and blood ceruloplasmin level[3,4].

Serum ceruloplasmin less than 20 mg/dL (1.49 µmol/L) may be consistent with the diagnosis. However, its positive predictive value is low (5.9%), and additional confirmatory testing is needed[3,4].

Serum copper is not very useful in diagnosing WD because it is variable and usually parallels ceruloplasmin. The 24-hour urine copper measurement more significant than 100 µ g/24 h (1.6 µ mol/24 h) is conventionally considered diagnostic of WD. Urinary copper values less than 40 or 50 µg (0.64 or 0.8 µmol)/24 h exclude WD. Liver biopsy with measurement of quantitative Copper is considered the gold standard for confirming the diagnosis and may even be necessary in patients with predominantly hepatic presentation. If available, genetic testing for ATP7B can be done[3,4].

5 TREATMENT

First-line treatment for WD is D-penicillamine, a copper chelator that will increase urinary excretion of the metal deposited in the tissues. Pyridoxine should be administered together with D-penicillamine. The 24-hour urine copper measurement is used to confirm chelation and increase your excretion. Trientine is the second-line treatment for individuals who cannot tolerate D-penicillamine[3,4].

Orthotopic liver transplantation is reserved for individuals who do not respond to medical therapy or cannot tolerate it due to severe adverse effects. It is also prudent to restrict foods with a high concentration of copper, such as viscera (liver, brain), chocolate, mushrooms, shellfish, and nuts[3,4].

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