v. 4, n. 68, 2024

International Journal of Health Science

WILSON'S DISEASE: A REVIEW OF TWO CLINICAL CASES AND LITERATURE REVIEW

Maria Elizabeth Bonorino Bortolanza
``Universidade Franciscana``, medicine course, Santa Maria - RS
ORCID: 0009-0001-9116-1533

Juliana Oliveira Freitas Silveira
``Universidade Franciscana``, neurologist doctor, Santa Maria – RS
ORCID: 0000-0001-7469-2482

Bruno Weis
``Universidade Franciscana``, medicine course, Santa Maria - RS
ORCID: 0009-0009-5398-8052

Gabriela Gomes Bento
``Universidade Franciscana``, medicine course, Santa Maria - RS
ORCID: 0009-0004-1569-8074

Deborah Knebel
``Universidade Franciscana``, medicine course, Santa Maria - RS
ORCID: 0009-0009-2974-6117

Luize de Faria Correa Roncato
``Universidade Franciscana``, medicine course, Santa Maria - RS
ORCID: 0009-0009-3823-6688

Luiza Caffarate Sarturi
``Universidade Franciscana``, medicine course, Santa Maria – RS
ORCID: 0000-0003-4675-5647

Abstract: Wilson's disease, also known as hepatolenticular degeneration, is a rare genetic disease of copper metabolism. Its basic pathophysiology is a mutation in the ATP7B gene, which results in a defective protein for the transport of this metal. As a result, excessive accumulation of copper occurs in the body, especially in the brain and liver, causing neurological, psychiatric, ophthalmic and hepatic symptoms. Thus, clinical presentations are varied and the diagnosis represents a challenge for health professionals, as it is not always obtained in a simple way, requiring a high level of suspicion and inclusion of Wilson's disease in the list of differential diagnoses in patients with presentations complex clinics. Although difficult, the diagnosis is extremely important, as at the same time, the institution of treatment prevents the onset of a degenerative and debilitating condition. In this context, the present work aims to report two clinical cases of patients with Wilson's disease, in addition to carrying out a narrative review of the literature on the topic.
Keywords: Wilson's disease; hepatolenticular degeneration; copper metabolism.

INTRODUCTION

Wilson disease (WD) is a rare, autosomal recessive genetic disorder first described by Samuel Alexander Kinnier-Wilson. The fundamental abnormality of this disease is impaired biliary excretion of copper, which leads to the gradual accumulation of this metal initially in the liver, and can also be deposited in other organs, such as the brain (Pfeiffer, 2016).

This disease is associated with hepatic, neurological and/or psychiatric symptoms that usually begin in the second or third decade of life, with a wide reported range extending from 6 to 72 years of age.

Symptoms that are usually present at the beginning include movement disorders, such as dystonia or parkinsonian symptoms, with emphasis on tremors, which can occur at rest or in action, with tremors described as "flapping of wings" being classic (Pfeiffer, 2016; Schwendimann et al., 2017).

Regarding its epidemiology, WD is present throughout the world, with men and women being equally affected. The estimated prevalence of WD varies between 1:30,000 and 1:100,000, being higher in some populations, such as on the island of Crete (1/11 live births), possibly due to consanguinity. Recent studies from the United Kingdom point to a prevalence of 1:7,000 (Coffey, 2010; Litwin, 2011).

CASE 1

Female patient, 20 years old, with Wilson's disease diagnosed on August 12, 2021, sought neurology outpatient care for follow-up. She reported that six months before the diagnosis, she had difficulty moving her left hand and muscle spasms in the upper limbs, in addition to dysphagia and dysarthria, progressing to muscle rigidity and dystonia. She sought care four months after the onset of symptoms and was referred to a hospital for hospitalization and diagnostic clarification.

On admission on August 5, 2021, he reported recurrent and painful muscle contractions without loss of consciousness. On physical examination, she had dysarthria and pain during muscle spasms. On oroscopy, absence of ulcers on the lips and oral cavity. General physical examination (palpation of the abdomen, cardiac and pulmonary auscultation) was normal. The neurological examination showed generalized dystonia of greater intensity in the left hemibody, with contractures, preserved strength in the right hemibody and grade IV in the left hemibody. Sensitivity was preserved and there were no pyramidal signs.

Laboratory and imaging tests prior to admission were normal, except for changes in magnetic resonance imaging (MRI) of the brain, which showed symmetrical and bilateral areas of high signal on T2/FLAIR, in the putamen, caudate nuclei, ventrolateral thalami, and splenium of the body. callosum, cerebral peduncles, mesencephalic tegments and middle cerebellar peduncles, suggesting a metabolic or toxic etiology. The hypothesis of Wilson's disease was considered.

The ophthalmological examination revealed, through biomicroscopy, a ring suggestive of copper deposits in the Descemet's membrane in the superior and temporal cornea in both eyes, compatible with Kayser-Fleischer rings. The diagnosis of Wilson's disease was confirmed with low levels of ceruloplasmin (less than 10mg/dl), presence of hemolytic anemia with negative Coombs, suggestive neurological symptoms, in addition to a Leipzig score of 6. Treatment was then started with D- penicillamine and subsequent dose adjustments.

A liver biopsy was performed on August 16, 2021, which demonstrated chronic hepatitis with mild portal and lobular activity, minimal interface hepatitis, with very focal macrogoticular steatosis.

During hospitalization, the patient had complications such as pulmonary and urinary sepsis, requiring care in an intensive care unit, in addition to having pancytopenia. Therefore, the hypothesis of medullary aplasia due to medication was raised, with suspension of D-penicillamine and subsequent hematological improvement. After that, the medication was restarted and a gastrostomy was performed. She was discharged from hospital on November 3 after three months of hospitalization, where she received multidisciplinary care.

During outpatient follow-up until May 2022, the patient reported significant improvement, being able to communicate better and eat without assistance. She continued to use several medications and presented, on physical examination, dystonia involving the cervical region and four limbs, with greater intensity in the left hemisphere, but with evident improvement after botulinum toxin. Strength was preserved in the right hemibody and left hemibody, grade IV. Dystonia did not allow adequate assessment of coordination.

The patient presented increased muscle tone, associated with global bradykinesia, without evidence of tremor. She remained under follow-up at the neurology outpatient clinic.

CASE 2

Female patient, 22 years old, sought care at a neurology outpatient clinic in September 2021 to investigate headache and syncope.

Three months earlier, she presented with severe headache and loss of consciousness. After waking up, she noticed a deviation in lip rhyme, loss of strength in all four limbs and sought emergency care, where carbamazepine was started. One month before the appointment, she underwent laboratory tests, brain MRI, electroencephalogram and started lamotrigine.

From the beginning, he developed dysarthria, paresis in the right upper and left lower limbs, memory changes, inattention and dyspnea. The mother reported episodes in which the patient was "out of breath" with fixed gaze, lasting minutes. Three days before the appointment, she had a new syncope with nausea and headache for 15 minutes. The mother denied hypertonia, clonic movements or release of sphincters.

At the first consultation, she had a history of anemia and neutropenia, both with spontaneous resolution, in addition to chronic thrombocytopenia. The neurological examination showed normal cranial nerves,

preserved trophism and muscle tone, grade V strength in the limbs, atypical gait and normoactive reflexes. There was mild apraxia in motor coordination movements. A new brain MRI with contrast and electroencephalography were requested and lamotrigine was increased to 100 mg/day, in addition to clobazam 5 mg at night.

Two months later, she complained of tremors in her hands, weakness in her right hand and leg, and headache attacks characteristic of migraine with visual aura. The MRI showed signal changes symmetrically affecting the middle cerebellar peduncles, cerebellopontine tracts, periaqueductal white matter, rostro-lateral portion of the thalamus and the basal ganglia. From this point onwards, it was considered Wilson's disease.

In February 2022, she had a new syncope with loss of tone, confusion, aggression, repetitive movements in the upper limbs and dysarthric, bizarre, incoherent and disjointed speech. She denied memories of the incident and similar episodes. She mentioned partial improvement of the tremors. She was undergoing psychological counseling due to irritable and anxious mood, in addition to motor physiotherapy.

The physical examination showed Kayser-Fleischer rings, slurred speech, mild Parkinsonian gait, resting tremor on the right, strength grade V on the right and IV on the left, postural instability and a positive pull test. Treatment for Wilson's disease was started with D-penicillamine and zinc acetate.

Laboratory tests in March 2022 showed low ceruloplasmin (< 8), normal blood count, platelets of 114,000, negative indirect Coombs, normal electrolytes and liver enzymes, serologies for hepatitis B, hepatitis C, HIV and VDRL non-reactive, 24-hour urinary copper 908 (reference value: 15-60).

Until August 2022, he continued to have parkinsonian gait, but with improvement. Hand tremors were mild. It improved scandi speech, apraxia and dysphagia. Limb strength was grade V. Pull test was positive and Romberg's test was negative. He reported improvement in anxiety symptoms with the use of desvenlafaxine 50 mg and mirtazapine 15 mg at night. He was undergoing nutritional monitoring, with diet adjustments according to specific WD restrictions.

DISCUSSION AND LITERATURE REVIEW

PATHOPHYSIOLOGY OF WILSON'S DISEASE

Wilson's disease is caused by an autosomal recessive mutation in the ATP7B gene, responsible for encoding an ATPase protein of the same name, which resides in the trans-Golgi network in the liver and transports copper across organelle membranes, allowing the incorporation of copper into apoceruloplasmin to form ceruloplasmin.

Under normal conditions, ceruloplasmin would be excreted in bile with copper bound to it, functioning as the main route to remove excess copper from the body and ensure the body's homeostasis (Mulligan et al., 2020; Pfeiffer, 2016).

However, as this protein is defective, copper accumulates in hepatocytes and subsequently reaches the bloodstream. There, copper exists in two forms: bound to ceruloplasmin and not bound to ceruloplasmin (free copper). In physiological situations, the portion of copper bound to ceruloplasmin accounts for the largest part, while free copper accounts for the smallest (around 5-15%). In contrast, in WD, serum levels of ceruloplasmin are reduced, precisely due to the lack of incorporation of copper into apoceruloplasmin, which would be the portion not bound to copper (Mulligan et al., 2020).

As a result of this pathophysiology, there are harmful consequences in multiple organs and systems. In the liver, it results in steatosis, fibrosis, portal hypertension, variceal bleeding and encephalopathy. In the brain, it affects astrocytes and the blood-brain barrier. In skeletal muscle and heart, it leads to rhabdomyolysis and cardiomyopathy. In the joints, it causes osteoarthritis. In the kidney, free copper is excreted in the urine, which can cause renal tubular dysfunction or renal failure. (Scheiber et al., 2017).

CLINICAL MANIFESTATIONS

Symptoms of WD usually appear in the second or third decade of life, typically before the age of 30 and almost always before the age of 40, although there are reports of patients who developed symptoms at the age of 70. At the time of diagnosis, signs and/or symptoms may be present, mainly hepatic, neurological, psychiatric and ophthalmic (Mulligan et al., 2020; Pfeiffer, 2016; White, 2014). There are some clinical manifestations considered typical of WD and worth highlighting, as shown in the Table below:

Clinical feature	Findings
Ocular	Kayser-Fleischer rings
Neurological	Dysarthria, ataxia, dystonia, tremor, parkinsonism, choreoathetosis, cognitive impairment, seizures, myoclonus, autonomic dysfunction
Neuropsychiatric	Depression, personality change, anxiety, psychosis
Liver disease	Asymptomatic biochemical abnormalities, acute transient hepatitis, chronic active hepatitis, cirrhosis, fulminant hepatic failure

Table 1: Typical clinical features of Wilson's disease

Source: Neurological manifestations of acute and chronic liver diseases (White, 2014)

DIAGNOSIS

Due to the numerous forms of presentation of WD, the diagnosis is not always obtained easily. In general, the presence of Kayser-Fleischer rings, typical neurological symptoms and/or a low serum level of ceruloplasmin (<0.1 g/L) is sufficient to establish a diagnosis, however, in most cases, the association of clinical manifestations and laboratory parameters is necessary (Ferenci, 2017).

Thus, in 2001, in Leipzig (Germany), the Leipzig criteria scoring system was created, during the 8th International Meeting on Wilson's disease and Menkes' disease. This system uses clinical, biochemical and, for the first time, molecular genetics to determine the diagnosis of WD. Its use has been validated in adult and pediatric populations and incorporated into the guidelines presented by the European Association for the Study of the Liver (Schilsky, 2017).

TREATMENT

After the diagnosis of WD, treatment must be continued for life. It is divided into: (1) treatment of symptomatic and (2) asymptomatic patients. The difference is in the objective, in the first category it is to reverse the copper-related injury and, in the second, to prevent symptoms. (Schilsky, 2017).

Therefore, copper removal is done with powerful chelators, D-penicillamine and trientine. Trientine, traditionally used as a second option for those intolerant to D-penicillamine, can also be the first choice due to the lower incidence of side effects. However, there are no studies directly comparing these agents, leaving the choice at the discretion of the doctor. (Wiggelinkhuizen et al, 2009).

Patients with symptoms, regardless of whether they are hepatic, neurological and/or psychiatric, must receive chelation therapy. In asymptomatic patients, chelation therapy

can be instituted with the drugs already mentioned above, in a reduced dose or zinc salts (Schilsky, 2017).

Other aspects of treating patients with WD include additional therapy of neurological and psychiatric symptoms with a view to improving quality of life. Furthermore, a multidisciplinary approach involving speech therapy for patients with dysarthria and dysphagia, as well as nutritional therapy for all patients, is extremely important (Mullingan et al, 2020).

DISCUSSION

WD is usually diagnosed between the ages of 5 and 35, with an average of 13 years. Patients in case 1 and 2 were diagnosed at 20 and 22 years old, respectively, data compatible between Lin et al., Stremmel W. et al. and Wiernicka et al.

According to Lorincz, neurological manifestations are more common in adolescent and adult patients, with an average age of presentation for these symptoms between 15 and 21 years, in addition to being present as an initial form of WD in up to 68% of the time. Both cases described in this work had neurological manifestations as the beginning of the disease and corroborate the data by *Lorincz, Saito T., and Ferenci P. et al.*

Dysarthria was found in 85 to 97% of patients with neurological WD, a manifestation evident in both patients. However, the patient in case 1 presented with spastic dysarthria, a variation that, according to Lorincz, is commonly seen in patients with WD. On the other hand, the patient in case 2 presented scandi/ataxic speech, also common in WD.

When it comes to dystonia, the predominant finding in case 1, according to *Lorincz*, can range from mild to debilitating. In this patient, severe dystonia was seen, which caused difficult-to-control pain, requiring opioids for pain therapy. In comparison, the patient in case 2 only presented dysphagia as a manifestation of dystonia, which was not as significant as in case 1.

Wilsonian tremor is present in more than 50% of cases, however the patient in case 1 did not present this symptom, while the patient in case 2 presented unilateral isolated resting tremor, considered atypical for WD, according to *Lorincz*.

In WD parkinsonism, bradykinesia, gait abnormalities and impairment of rapid alternating movements are typical according to *Schwendimann*, and was evidenced in the case of patient 2, who presented parkinsonian gait and ataxia in motor coordination movements. Despite this, the patient in case 1 did not demonstrate any signs of parkinsonism and did not have her motor coordination capacity assessed due to intense dystonia.

As for psychiatric symptoms, according to Pfeiffer, most reports indicate that they are evident in approximately 30 to 40% of individuals with WD and can range from subtle personality changes to frank psychosis. However, the patient in case 1 did not present any psychiatric manifestation, unlike the patient in case 2, who had an episode of agitation associated with confusion and, despite it being an isolated event, the patient continued to present an irritable and anxious mood, which is why he maintained psychological support and used medication to control it.

Regarding liver symptoms, according to Ferenci P., some degree of liver disease is generally present at diagnosis. The patient in case 1 had chronic hepatitis and steatosis, while the patient in case 2 had no liver symptoms and no biopsy was performed.

The hepatic manifestations of individuals with WD range from asymptomatic biochemical abnormalities to signs and symptoms of steatosis, acute hepatitis, acute

Feature	Patient, case 1	Patient, case 2
Age at diagnosis	20 years	22 years
Neurological manifestations		
Dysarthria	Spastic type	Scandi type
Dystonia	Present and serious	Absent
Dysphagia	Present	Present
Tremor	Absent	Present at rest
Parkinsonism	Absent	Present
Psychiatric manifestations	Absent	Present (irritability and anxiety)
Ophthalmological manifestations	Present	Present
Kayser-Fleischer rings		
Liver manifestations	Present in Histology	Absent (no liver biopsy was performed)
Serum ceruloplasmin (mg/dL)	< 10	< 8
Copper in 24-hour urine	Superior to 250mcg	908
Neuroimaging findings	Present and characteristics	Present and characteristics
Time to diagnosis	6 months	Months

Table 5: Comparison between patients in the cases reported in this work

liver failure, chronic hepatitis and cirrhosis. Changes may include abdominal pain, jaundice, hepatomegaly and splenomegaly, which are absent in the cases. Laboratory findings include a low level of serum ceruloplasmin, present in both cases, thrombocytopenia, which was present in the past history of the patient in case 2, and Coombs-negative hemolytic anemia, present in case 1 and present in the past pathological history of the patient in the case. two.

Regarding ophthalmic manifestations, there are two classic findings of WD. Kayser-Fleischer rings, formed by the deposition of copper in the cornea, are the most common finding, generally golden, brown or green in color, almost always present bilaterally. The other finding is sunflower cataract, which consists of copper deposition in the sunflower-shaped anterior capsule, present in 2 to 17% of patients.

The two patients in this study presented Kayser-Fleischer rings, confirming the data from Lorincz and Pfeiffer, who state that almost 100% of patients with neurological dysfunction present this finding.

Neuroimaging findings were crucial for the diagnosis of WD in both cases. The MRI of the patient in case 1 showed areas of high signal on T2/FLAIR, while that of the patient in case 2 showed low signal on T1 and high signal on T2. In other words, both exams contained findings highly suggestive of WD, as described by Pfeiffer, Lorincz and Ferenci.

To diagnose WD, Kayser-Fleischer rings, neurological symptoms and a low serum level of ceruloplasmin are sufficient. Both patients had these findings and scored 7 in the Leipzig criteria, applied retrospectively with the information available, confirming the diagnosis, which is established from 4 points.

Finally, the treatment of WD consists of removing accumulated copper with chelating agents - D-penicillamine and trientine - and preventing reaccumulation with smaller doses of these agents or zinc salts. Patients in cases 1 and 2 initially received D-penicillamine, considered by Brewer to be the most effective in copper efflux, but also the most associated with side effects, as pointed out by Weiss et al., including bone marrow suppression, suspected in this case. 1. Both patients also received zinc salts to prevent copper absorption.

Furthermore, it is worth mentioning the additional treatments that both patients needed due to their neurological manifestations. The patient in case 1 required the application of botulinum toxin to treat intense dystonia and the patient in case 2, a dopaminergic agonist to control parkinsonism, associated with a serotonin and norepinephrine reuptake inhibitor for anxious symptoms.

CONCLUSION

This work illustrates, through two cases of patients with Wilson's disease with neurological manifestations, the significant impact on the quality of life of patients affected by this disease. Unlike other neurodegenerative diseases, Wilson's disease is treatable and controllable. However, patients with this pathology who present essentially neurological and/or psychiatric symptoms still frequently suffer from delays in diagnosis. In this context, the recognition of Wilson's disease requires a careful look from the doctor so that the diagnosis can be made as soon as possible and the appropriate treatment can be instituted, with the aim of making the prognosis more favorable for each patient.

The importance of further studies on the topic is also highlighted, given that the available therapies, despite being indispensable, still have limitations.

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