

Something's Happening...I'm Not Who I Used to Be

Shannon Daniel, B.Sc. (OT7), Faculty of Medicine, University of Toronto
 Mike Humphreys, MD, Faculty of Medicine, University of Toronto

Case Presentation

A 19-year old female presented to emergency with a four-month history of tremor, progressive dysarthria, and dysphagia. The patient first noticed that she was drooling excessively; this was followed by difficulty speaking and, soon thereafter, by difficulty with swallowing both solids and liquids. She also noticed progressive weakness in her left leg with painful spastic toes that made walking difficult. She denied any headache, visual disturbances, urinary, or bowel incontinence. Collateral history revealed personality changes and recent emotional lability.

What are the Differential Diagnoses?

The patient presents with a progressive movement disorder and has symptoms of dysarthria, dysphagia, tremor, and motor weakness. The differential for movement disorders include Parkinson's syndrome, Parkinson's disease, essential tremor, Huntington's disease, progressive supranuclear palsy, multiple sclerosis, Wilson's disease, and multiple system atrophy. Stroke, seizures, and neoplasm should also be ruled out.

The patient stated that she had recently seen a neurologist with regard to her distressing symptoms. He ordered a brain MRI, and the results suggested a metabolic etiology. Consequently, she was advised to come to the hospital for further work-up.

In light of this new finding, what diagnosis must you consider?

In any young patient presenting with a progressive movement disorder and an MRI suggestive of metabolic etiology, the diagnosis of Wilson's disease must be ruled out.

What is Wilson's disease?

Wilson's disease (WD), also known as hepatolenticular degeneration, is a rare autosomal recessive disease involving copper metabolism. It has an incidence of 1 in 30,000 people. Kinnear Wilson first described WD in 1912, but it was not until 1993 that the gene responsible for WD was identified. The gene, ATP7B, encodes a metal transporting P-type ATPase, which is mainly expressed in hepatocytes and functions in the transmembrane transport of copper.¹ Absent or reduced function of this gene leads to decreased hepatocellular excretion of copper into bile. Consequently, copper accumulates in the liver, leading to cellular necrosis and leakage into the bloodstream. The excess copper is deposited in various other organs, notably the brain, kidney, and cornea, and this process most commonly manifests as liver disease, neuropsychiatric symptoms, or Kayser-Fleischer (KF) rings in the eye.

Back to the Case

Past medical history was non-contributory. Her family history was positive for early-onset dementia (mother, diagnosed in her early fifties), and Alzheimer's dementia (maternal grandmother, diagnosed in her sixties). Her mother presented with forgetfulness, tremulousness, social dysfunction, personality changes, and progressive speech difficulty. Unfortunately, a formal diagnosis had not been established due to patient non-compliance.

What is the significance of the patient's family history?

When considering the diagnosis of WD, family history is an important clue because WD is an autosomal recessive disease. As such, in order to inherit WD, both of the patient's parents must be at least carriers of the gene. Therefore, the likelihood of finding a homozygote amongst the siblings is 25% and amongst the children 0.5%.²

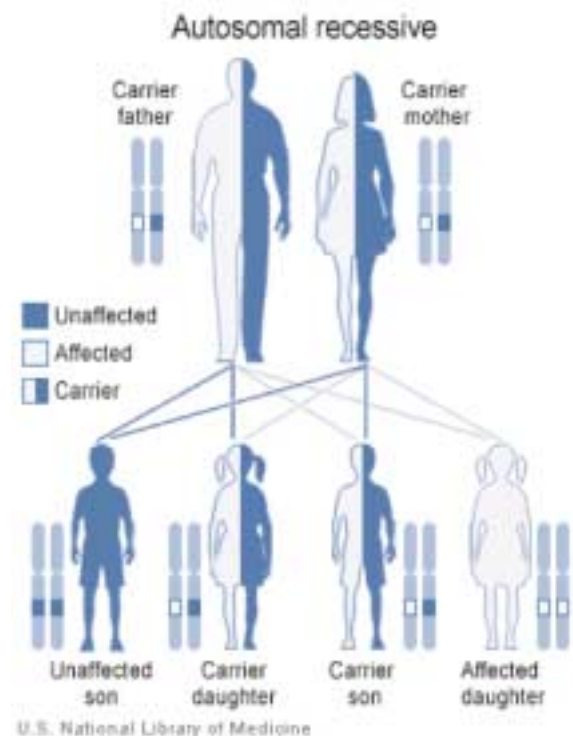


Figure 1. Inheritance of an autosomal recessive disease (e.g. WD)
 Source: <http://ghr.nlm.nih.gov/handbook/illustrations> Author: ghr.nlm.nih.gov
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How do patients with neuropsychiatric manifestations of Wilson's disease present?

Neurological symptoms usually develop during the mid-teens to early thirties, but there are documented cases of patients ranging from 45 to 55 years who present with late neurological disease.³ Initial symptoms are subtle and usually involve speech, mild tremor, and writing difficulties. Typically, at first, speech is slurred and hypokinetic, and during the course of the disease, more pronounced speech defects occur. Tremor can be of any type including resting, postural, or kinetic.⁴ Dystonia is not uncommon and mainly affects the facial muscles, often leading to excessive drooling. As the disease progresses, dystonia in the back, neck, or extremities contributes to painful contractures. Patients often mimic Parkinsonian symptoms, exhibiting rigidity, bradykinesia and occasionally micrographia. Incoordination is a common symptom as well, and is evident when assessing gait.

One third of patients present, initially, with psychiatric abnormalities such as hyperkinetic behaviour, irritability, emotional lability, psychosis, mania, difficulty concentrating, or personality changes.² Often, these patients are mistakenly diagnosed with a primary psychiatric disorder and are referred for psychotherapy.

KF rings are present in 95% of patients with neurologic presentation.² KF rings are golden or greenish-brown rings, are found in Descemet's membrane in the cornea of the eyes, and are due to copper deposition.

The hallmark of neurological WD is a progressive movement disorder characterized by dysarthria, dysphagia, apraxia, and a tremor-rigidity syndrome.²

Back to the Case

Examination demonstrated marked dysarthria. Generalized tremors were evident. The patient was distressed and embarrassed by her symptoms. A detailed neurological exam was performed. Pupils were equal and reactive to light, with normal accommodation. Her visual fields and funduscopy exam were normal. Extra-ocular movements were normal, but slow, subtle saccades were noted when looking to the right. There was no nystagmus identified. All other cranial nerves were grossly normal. She had a normal sensory exam. On motor exam, she had increased tone bilaterally. Power was 5 out of 5 (Medical Research Council Scale) in upper and lower limbs. Reflexes were 2+ bilaterally. Left foot was slightly dorsiflexed and everted with contracture of the 2nd to 4th digits. Plantar response was downgoing. Tests for coordination showed no dysdiadochokinesis or pronator drift. Her gait was slow with decreased arm swing and left foot drop.

What investigations would help confirm a diagnosis of Wilson's disease?

A CT or MRI of the brain should be considered in any patient that presents with unexplained neurological symptoms. Structural abnormalities in the basal ganglia, albeit not specific for WD, are evidence for metabolic disease¹ and thereby warrant a work up for WD.

The diagnosis of WD may involve one or more of the following laboratory tests, findings or procedures:

1. Unusually low serum ceruloplasmin levels.

2. 24-hour urinary copper excretion test with findings greater than 1.57 $\mu\text{mol}/\text{day}$.
3. Serum copper levels less than 12.5 $\mu\text{mol}/\text{L}$.
4. Levels of copper in the liver of over 250 $\mu\text{g}/\text{g}$ dry weight. Tissue samples for testing are obtained through a surgical biopsy of the liver. [Gold Standard]
5. Confirmation of the presence of Kayser-Fleischer rings by slit lamp exam²

Since neurological presentation of Wilson's disease is often associated with concomitant liver disease, it is important to order liver enzyme (AST, ALT, ALP) and function (platelet count, INR, albumin, and bilirubin) tests to look for signs of liver involvement.

Investigations

The results of hematologic and biochemical tests on admission are provided in Table 1.

Hematologic	Biochemical
Hb 138 g/L (120-160)	Na 127 mEq/L (136-144)
WBC 6.7 (3.8-10.8 $\times 10^9/\text{L}$)	K 5.3 mEq/L (3.5-5.1)
Platelets 182 (130-400 $\times 10^9/\text{L}$)	Bicarbonate 16 mEq/L (18-23)
Vitamin B12 346 pmol/L (> 156)	Cl 100 mEq/L (100-108)
TSH 4.67 mIU/L (0.35-5.50)	AST 3 U/L (0-35)
	ALT 15 U/L (0-35)
	ALP 63 U/L (30-120)
	Amylase 29 U/L (20-125)
	Bilirubin 9 $\mu\text{mol}/\text{L}$ (5-17)
	Ceruloplasmin 0.04g/L (0.2-0.6)
	Cu plasma 5.9 $\mu\text{mol}/\text{L}$ (11-24.4)
	Cu timed urine 1.91 $\mu\text{mol}/\text{CP}$ (0.06-0.28)

Table 1. Laboratory results

CT of the brain showed evidence of posterior fossa atrophy. Bilateral symmetrical areas of hypodensity were noted to involve basal ganglia as well as slit-like areas along the lateral aspect of the basal ganglia, on both sides, suggestive of a metabolic etiology.

Ophthalmology was consulted, and slit lamp examination revealed Kayser-Fleischer rings in Descemet's membrane.

With a ceruloplasmin level of 0.04 and presence of KF rings, a diagnosis of WD was established. The patient had no evidence of associated liver disease.

What is the current recommended drug therapy for WD presenting with neurological disturbances?

Penicillamine was formerly the drug of choice for treating WD. However, more recent studies have shown that penicillamine has a high rate (estimated at approximately 10-50%) of causing neurologic worsening. About half of the patients whose condition worsens never recover to their pre-penicillamine baseline.

The current first-line therapy recommended for patients with WD presenting with neurologic signs and symptoms is tetrathiomolybdate (TM) for eight weeks, followed by zinc maintenance therapy.^{5,6} In contrast to penicillamine therapy, the rate of neurological deterioration with TM is less than 5%. The main disadvantage of TM is that it is not yet commercially

available. If unavailable, the second choice is zinc therapy alone, followed by the third choice: namely, trientine.^{5,6}

What other steps can be taken in WD management?

Lifestyle modifications: Patients should be advised to follow a low-copper diet. Liver and shellfish contain high levels of copper and should be avoided. Copper levels in drinking water could also be evaluated before consumption since copper from pipes can leach into the water.⁵

Physical rehabilitation: This is very important in neurological patients to maintain functional mobility. In patients that develop contractures, physical therapy will help improve range of motion and mobilize joints.

Follow up: A neurologist should follow patients with neurological symptoms to monitor for adequate drug therapy and improvement in symptoms. Patients should also have urinary copper excretion and plasma levels measured annually.

Family screening: If a patient is diagnosed with WD, it is imperative that his or her first-degree relatives be screened for WD. In addition to regular work up, haplotype studies can also be done.¹

Will this patient get better?

Fortunately, yes. Neurological patients with WD begin to improve clinically 5 to 6 months after initiation of therapy. This improvement continues over the subsequent 18 months.¹ Residual abnormalities present after 2 years of adequate anti-copper therapy are usually permanent.¹ Psychiatric

and behavioural symptoms usually improve along with neurological symptoms.

Epilogue

The patient was referred to neurology and started on Zinc therapy. Merely 6 weeks after initiation of treatment, the patient started to show signs of improvement.

Conclusion

Although WD is a rare metabolic disorder, physicians should maintain a high index of suspicion for this disease in young patients presenting with neuropsychiatric symptoms, because it is lethal if unrecognized and untreated. With timely recognition, diagnosis, and initiation of treatment, patients can significantly improve, and severe permanent damage can be prevented.

References

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