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# ANALYSIS OF WILSON DISEASE – A NEUROLOGICAL PERSPECTIVE

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## ABSTRACT

**Introduction:** Wilson disease (WD) is autosomal recessive disorder of copper metabolism. Wilson disease patients usually suffer from hepatic or neuropsychiatric complications. The symptoms appear between ages five to 35 but it can vary from two years to 72 years. **Materials and Methods:** Study was carried out in department of neurology at Madurai medical college. This study included 13 cases of WD to determine clinical presentation, diagnostic findings (including laboratory results) and neurological presentation. It included 13 patients who presented with hepatic manifestations and/or Neuropsychiatric manifestations and/or family history suggesting features of WD. Patients with hepatitis B and C and those with history of taking antipsychotic drugs were excluded from the study. Patient's data was included in a well-designed proforma. Liver function test, serum ceruloplasmin, blood complete picture was analyzed. **Results:** There were eight male and five female patients with evidence of various manifestations here (i) hepatic in which they had only liver dysfunction (ii) hepatic and neurological (iii) neurological. The mean age of presentation was 22.6 ±9.83years (range 13-51 years). Decreased serum ceruloplasmin were confirmed in all patients and Kayser–Fleischer rings (KF rings) in all patients. High degree of suspicion leads to early treatment with good outcome. **Conclusions:** The WD is rare but important cause of chronic liver disease and neurological illness. Clinical and biochemical analysis in cases of patients with unexplained neuropsychiatric symptom with high degree of suspicion can lead to early treatment with good outcome.

**KEYWORDS:** Hepatic, neurological, neuropsychiatric disorder, Wilson disease.

## INTRODUCTION

Wilson's disease (WD) is an autosomal recessive disease characterized by accumulation of intracellular copper in the liver and central nervous system.[1] It most frequently affects children and young adults. Patients present with a variety of clinical symptoms depending upon the most severely affected organ (e.g., acute liver failure, cirrhosis, neurologic or psychiatric syndromes).[2,3] It runs an always fatal course if not effectively treated by chelating agents.[4] The clinical manifestations of WD are extremely diverse. In the first decade of life patients presents more frequently with hepatic manifestations. After the age of 20 years 75% of patients present with neurological manifestations and 25% with both hepatic and neuropsychiatric manifestations.[5] The Leipzig WD diagnostic scoring system is useful in supporting an initial diagnosis of WD.[6,7] This scoring system, proposed by the European association for the study of the liver, is in use prior to confirmatory mutation analysis.

The current treatments for WD are chelating agents (D-penicillamine, trientine and tetrathiomolybdate) and zinc salts. On the whole, the approach for treatment depends on whether the patient is asymptomatic or symptomatic, and also on the main manifestation of the symptoms (neurological and hepatic).[8] Patients with acute liver failure or with decompensated cirrhosis that is unresponsive to chelation treatment should be treated with liver transplantation.

Neurological dysfunction constitutes the initial clinical manifestation in 40–60% of individuals with Wilson's disease.[9] The average age of symptom onset in persons who present with neurological dysfunction is 18.9 years, although neurological symptoms may appear as early as age 6 years[10] On the other end of the age spectrum, onset of neurological symptoms as late as age 72 years has been described.[11] Tremor, which may be resting, postural, or kinetic, is the most frequent initial neurological feature of Wilson's disease. Proximal upper extremity tremor may take on a coarse, ''wing-beating'' appearance, but Wilson's disease tremor may also be distal and quite small in amplitude. Head titubation may also appear. The many guises that Wilson's disease tremor may assume make it important to consider and exclude the possibility of Wilson's disease in any individual, but especially young persons, with tremor. Dysarthria is also common in persons with Wilson's disease and may possess either an extrapyramidal or a cerebellar character. Dystonia involving the tongue, face,

and pharynx may produce not only dysarthria, but also drooling and an unusual perturbation of facial expression that results in a frozen grimace (risus sardonicus). A peculiar ‘‘whispering dysphonia’’ has been described in Wilson’s disease, as has a laugh in which most of the sound is generated during inspiration.[12]

A variety of other neurological features may emerge in Wilson’s disease. Cerebellar dysfunction develops in approximately 25% of individuals with neurological Wilson’s disease. Dystonia may be present in almost 40%. Gait abnormalities are a frequent component of neurological Wilson’s disease; both extrapyramidal and cerebellar patterns may develop. Chorea, tics, and myoclonus are unusual, although severe generalized myoclonus associated with extensive white matter lesions has recently been described.[13] The painless variant of painful legs and moving toes syndrome has also been reported in a person with Wilson’s disease. Although not often mentioned in reviews of Wilson’s disease, autonomic dysfunction is noted by some investigators to be present in 26 to 30% of persons with the disease.[14]

Seizures are an infrequent component of Wilson’s disease, but may occur in up to 6% of patients. Partial seizures occur most frequently, and benign epilepsy of childhood with centrotemporal spikes has been observed. Status epilepticus is rare, but does occur. Headache or seizure may occur in the setting of Wilson’s disease and may be the initial neurological symptom in approximately 10% of patients. Neither upper motor neuron nor lower motor neuron dysfunction is typically present in Wilson’s disease. However, peripheral sensorimotor polyneuropathy with both demyelinating and axonal involvement has been reported as the initial manifestation of Wilson’s disease.[15]

Olfactory impairment has recently been reported in persons with Wilson’s disease who have neurological dysfunction. The severity of the olfactory deficit parallels the severity of neurological dysfunction. Pseudobulbar emotional lability, hypersomnia, altered rapid eye movement (REM) sleep function, priapism, and muscle cramps have all also been noted in individuals with Wilson’s disease. The purpose of this study was to outline differences in the neurological spectrum of Wilson disease.

## MATERIALS AND METHODS

This study was approved by the ethical committee of Madurai medical college, Madurai where research was carried out. Patient’s data was recorded in a well designed proforma. Detailed family history was obtained along with pedigree pattern with emphasis on consanguinity.

Information regarding age, sex, mode of onset (hepatic, neurologic, psychiatric symptoms) was collected through a questionnaire. Liver function test, serum ceruloplasmin, blood complete picture were analyzed. The patients were examined in ophthalmology department to detect the presence of KF ring. Hepatic changes, features of portal hypertension, gall stones, and polyps were examined in radiology department by an abdominal ultrasound.

The diagnosis of WD was based on the presence of liver disease and at least two of the following criteria: (i) a positive family history; (ii) low ceruloplasmin (<20 mg/dl); (iii) elevated liver copper (>250 µg/g dry weight) (iv) presence of KF rings; (v) elevated 24--h urinary copper (>100 µg/24h); and coomb’s negative hemolytic anemia.

These criteria were complemented with the use of the quantitative evaluation scale of the Leipzig WD scoring system: a score of four or more being highly probable for WD diagnosis [Table 1]. Each of these patients had a score of at least three according to a scoring system based on clinical and biochemical parameters. In patients of WD, other causes of liver disease namely autoimmune and cholestatic liver disease, viral hepatitis, a1-antitrypsin deficiency and other metabolic liver disorders were excluded by appropriate investigations.

### Statistical Analysis

All data was analyzed using SPSS version 22.0. Quantitative data such as age, hemoglobin etc were expressed as mean with ± SD and quantitative variables such as sex, movement disorders, hepatic involvement etc were expressed as frequency and percentage.

## OBSERVATION AND RESULTS

There were eight male and five female patients with evidence of various manifestations here In patients the mean age of presentation was 22.6 ± 9.83 years (range 13-51 years) and 61% were male patients. Decreased serum ceruloplasmin and KF rings in confirmed in all of patients. The WD diagnostic score was greater than four in all patients. Hepatic involvement was seen in five patients. All patients were treated with chelating agents (D-Penicillamine) and zinc salts.

We evaluated the neurological symptoms in all patients. Akinetic rigidity was present in five patients (39%). Pseudosclerosis with tremor was seen in six patients (46%). Ataxia was seen in five patients (39%).Dystonia was seen in four patients (30%). In one male patient aged 18 choreoathetosis was seen. Cognitive impairement was seen in three cases (23%). Some sort of changes were seen in MRI in all cases.

To explain in detail about individual cases, the patient no.1 was 21 year old male with insidious onset slowly progressive tremulousness with unsteadiness of gait for 3 years, on clinical examination patient had KF ring, postural tremor, cerebellar signs like ataxic speech, limb incoordination, wide based gait. Patient had normal LFT and USG. Serum ceruloplasmin levels was 3mg/dl. On

CT brain hypodensity in basal ganglia was seen. In MRI brain t2w hyperintensity in caudate, putamen, globus pallidus and midbrain was seen.

The patient no.2 was 15 year old female with insidious, progressive difficulty in swallowing with drooling of saliva and aggressive behavior for past 2 years, on clinical examination patient had KF ring, Pseudobulbar features, drooling of saliva, open jaw, orpharayngeal dystonia and extrapyramidal rigidity was seen. Patient had normal LFT and USG. Serum ceruloplasmin levels was 2mg/dl. In MRI brain t2w hyperintensity in both basal ganglia, thalamus and midbrain was seen.

The patient no.3 was 15 year old male with difficulty in writing for 1 year, on clinical examination patient had KF ring, writing dystonia. Patient had normal LFT and USG. Serum ceruloplasmin levels was 7mg/dl. In MRI brain t2w hyperintensity in caudate, putamen and globus pallidus was seen.

The patient no.4 was 18 year old male with insidious onset progressive involuntary jerky movements involving entire body and limbs for 4 years, on clinical examination patient had KF ring, mild MR and choreoathetosis. Patient had normal LFT and on USG hepatomegaly was seen. Serum ceruloplasmin levels was 6 mg/dl. On CT brain hypodensity in both basal ganglia was seen. In MRI brain t2w hyperintensity in both caudate nucleus and putamen was seen.

The patient no.5 was 52 year old male with insidious onset slowly progressive slowness in all activities for 2 years 6 months, on clinical examination patient had KF ring, cognitive impairement, akinetic rigid syndrome. Patient had normal LFT and USG. Serum ceruloplasmin levels was 5mg/dl. On CT brain hypodensity in basal ganglia was seen. In MRI brain- t2w hyperintensity in caudate, putamen, globus pallidus and thalamus was seen.

The patient no.6 was 13 year old female with progressive difficulty in swallowing, slurring of speech for 4 years, on clinical examination patient had KF ring, oropharyngeal dystonia, dysarthria, vacuous smile, open mouth, drooling of saliva. Patient had normal LFT and USG. Serum ceruloplasmin levels was 5mg/dl.In MRI brain t2w hyperintensity in basal ganglia, thalamus and midbrain was seen.

The patient no.7 was 35 year old female with insidious onset, progressive ataxia for 4 years, on clinical examination patient had KF ring, postural tremor, wing beating tremor and gait ataxia. Patient had normal LFT and USG. Serum ceruloplasmin levels was 6mg/dl. In MRI brain t2w hyperintensity in caudate, putamen, globus pallidus and cerebellum was seen.

The patient no.8 was 24 year old male with insidious onset slowly progressive tremulousness with slowness of all activities for 3 years, on clinical examination patient had KF ring, postural tremor, wing beating tremor, cog wheel rigidity and parkinson gait. Patient had normal LFT and USG. Serum ceruloplasmin levels was 4mg/dl. In MRI brain t2w hyperintensity in both basal ganglia was seen.

The patient no.9 was 15 year old female with insidious onset slowly progressive difficulty in writing, swallowing difficulty and drooling of saliva for 3 years, on clinical examination patient had KF ring, pseudobulbar features, vacuous smile, drroling of saliva and writing dystonia. Patient had normal LFT and USG. Serum ceruloplasmin levels was 8mg/dl. In MRI brain t2w hyperintensity in caudate, putamen, globus pallidus and thalamus was seen.

The patient no.10 was 21 year old male with insidious onset slowly progressive tremulousness for 2 years, on clinical examination patient had KF ring, postural tremor, wing beating tremor, cogwheel rigidity and reduced arm swing. Patient had normal LFT and USG. Serum ceruloplasmin levels was 4mg /dl. In MRI brain t2w hyperintensity in both basal ganglia was seen.

The patient no.11 was 22 year old male with insidious onset slowly progressive tremulousness with ataxia for 3 years, on clinical examination patient had KF ring, postural tremor was seen. Patient had abnormal LFT and normal USG. Serum ceruloplasmin levels was 5mg/dl. In MRI brain t2w hyperintensity in caudate, putamen and midbrain was seen.

The patient no.12 was 23 year old female with tremor and ataxia for 2 years, on clinical examination patient had KF ring, postural tremor, cerebellar signs like ataxic speech was seen. Patient had abnormal LFT and normal USG. Serum ceruloplasmin levels was 4mg/dl. In MRI brain- t2w hyperintensity in caudate, putamen was seen.
The patient no.13 was 21 year old male with signs of ataxia for 4 years, on clinical examination patient had KF ring and ataxic gait were present .Hepatic involvement was seen. Serum ceruloplasmin levels was 5mg/dl. In MRI brain t2w hyperintensity in thalamus was seen.

**DISCUSSION**

Wilson disease is autosomal recessive disorder of copper metabolism. Most people have no known family history of the disease. Initial symptoms may be non-specific and might not be easily recognized, resulting in considerable diagnostic delay and imprecise clinical data. In our study, There were eight male and five female patients with evidence of various manifestations here In patients the mean age of presentation was 22.6 ± 9.83 years (range 13-51 years) and 61% were male patients. Decreased serum ceruloplasmin and KF rings in confirmed in all of patients. The WD diagnostic score was greater than four in all patients. Hepatic involvement was seen in five patients. All patients were treated with chelating agents (D-Penicillamine) and zinc salts. Similar

observation of two-thirds being male was made by Dastur et al,[16] in a major Indian series, while 20 of 22 cases reported by Jha et al[17], were male. The neurological manifestations of WD include rigidity, tremors, gait abnormalities and choreiform movements. In terms of the WD diagnostic score, 100% of our patients were positive (13/13). American association for the study of liver disease guidelines was very useful in the diagnosis in our patients. A serum ceruloplasmin concentration below 20 mg/dl was considered as one of the major diagnostic criteria. The serum ceruloplasmin level was less than 20 mg/dl in all patients. According to the AASLD recommendations all our patients were prescribed chelating agent (D-penicillamine), after having being diagnosed.

The neurological abnormalities of WD show marked variation in both type of presentation and severity, but can generally be classified into syndrome types based on predominant symptoms, such as tremor and ataxia, bradykinesia (parkinsonism-like), and dystonia. In many cases, classification of neurological features is challenging as patients can have various signs and more than one abnormality, each with a different level of severity.

The results of our study was similar to one another study where the most common individual neurological signs were dysarthria (73.6%), arms postural tremor (69.8–71.7%), impaired finger tapping (66.0%), impaired posture (66.0%), and reduced facial expression (66.0%) (Table 2). The syndrome of highest prevalence was ataxia/tremor (62.3%) followed by dystonia (15.1%) and parkinsonism (11.3%). A small proportion of patients (11.3%) had only discrete signs or were considered as unclassified.[18]

## CONCLUSION

Neurologic symptoms in WD are largely reversible with anti-copper treatment but most patients have at least minor residual neuropsychiatric impairment and approximately 20% of patients have unfavorable outcome with severe disability or death. The prognosis of WD is much better when treatment is started before neurologic symptoms develop.

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