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Wilson's disease: A study of 26 cases from south India

KEYWORDS

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ABSTRACT

Background : *Wilson disease is an inborn error of copper metabolism, which is potentially treatable. This disease has protean manifestations and patient may first present to a psychiatrist, neurologist or gastroenterologist. Early and correct diagnosis and institution of proper treatment and lifelong continuation can prevent devastating consequences as the disease is treatable.*

Aims and objective : *To describe the clinical presentation, biochemical, neuroimaging and therapeutic aspects of Wilson disease.*

Materials and methods: *Twenty six Wilson's disease patients from may 2015 to april 2016, were retrospectively evaluated according to their clinical presentation, biochemical parameters, neuroimaging, response to therapy and outcome.*

Results: *The study material included 12 males and 14 females with age ranging from 6 and 53 years respectively. The clinical syndrome included neurological in 8, followed by hepatic in 7 patients, combination of symptoms in 5, psychiatric and asymptomatic presentation in 3 patients each. Kayser-Fleischer rings were noted in 14 patients out of 26 patients. These rings were most prevalent in 7 patients with exclusive neurological manifestations followed by 4 patients with mixed disease presentation and 3 patients with exclusively hepatic symptoms. Serum ceruloplasmin levels ranged from 3.1 to 60.1 mg/dl and 22 (84%) out of 26 patients had serum ceruloplasmin levels < 20 mg/dl. 24 hour urinary copper (>100 µg/day) was increased in 17 (65%) patients with 24 hour urinary copper values varying from 26.16 µg/day to 2445.68 µg/day. Serum copper was low (<70mg/dl) in 23 (88%) patients with serum copper values ranging from 13.1mg/dl to 129.4mg/dl. 8 patients had basal ganglia hyperintensity on T2-weighted MRI images, 2 patients showed hyperintensities in the brainstem, 2 patients showed involvement of thalamus and 1 patient had simultaneous involvement of the basal ganglia, thalamus, and brainstem. All the 26 patients were treated with D-penicillamine. 4 patients had worsening of symptoms, skin rash was noted in 3 cases, gastrointestinal intolerance was observed in 1 patient and 2 patients developed thrombocytopenia. In these cases the drug was substituted with zinc sulphate (150-250 mg/day).*

Conclusion: *Wilson disease is treatable if correctly diagnosed, and an adequate quality of life can be achieved with treatment. High index of suspicion is required for an early diagnosis and proper management to prevent the disabling sequalae. Screening of all asymptomatic siblings for Wilson disease is a very important issue and must be carried out in all.*

Introduction

Wilson's disease is a rare inherited autosomal recessive inborn error of copper metabolism characterized by toxic accumulation of copper in liver, brain, cornea and other tissues. (1) In Wilson's disease, the processes of incorporating copper into ceruloplasmin and excreting excess copper into bile are impaired. The transport of copper by the copper-transporting P – type ATPase is defective secondary to one of several mutations in the ATP7B gene, which is localized in chromosome arm 13q. (2,3,4). The clinical manifestations of Wilson's disease are predominantly hepatic, neurologic, and psychiatric, with many patients having a combination of symptoms. (9) The diagnosis is confirmed by the measurements of serum ceruloplasmin, urinary copper excretion, and hepatic copper content, as well as the detection of Kayser-Fleischer rings (6) and determining the amount of copper in 1 g of dry liver specimen (7). At present, it has evolved from a uniformly fatal disease to a potentially treatable condition. Our understanding of the disease has progressed from the clinical description to biochemical and histological aspects and finally to the genetic basis of copper metabolism. Because of the drastically varied clinical presentation that leads to diagnostic difficulties, a number of aspects make the disease particularly interesting and important for neurologist, gastroenterologist and paediatricians. (8)

Materials & methods

The current study is a retrospective observational study between may 2015 to april 2016. Twenty six patients diagnosed with Wilson's disease in our institution were included in the study. The demographic features, clinical features, radiological manifestations, biochemical analysis and patients outcome were obtained from the medical records.

Symptoms of presentation were classified into hepatic, neurological, psychiatric, combination of symptoms or asymptomatic.

The diagnosis of the disease was based on clinical manifestations, positive history in the first degree relatives, exclusion of other apparent cause of the illness together with positive laboratory findings such as abnormal liver function tests, serum ceruloplasmin levels below 20mg/dl, and urinary copper levels above 100 µg/24 h, presence of Kayser-Fleisher ring by slit – lamp examination, decreased serum copper levels less than 70 mg/dl and suitable response to therapy. Neuroimaging (MRI/CT scan of brain) was performed only in patients with neurological, psychiatric and mixed presentations

All the patients did not undergo liver biopsy either due to coagulative disorders or because the procedure seemed unlikely to assist in the diagnosis of disease.

The patients underwent treatment with a daily dose of 1-2g of D-penicillamine and were recommended not to use foods containing high levels of copper.

Results

The study included 26 patients, 12 male and 14 female with the lowest and the highest age for appearance of this disease was 6 and 53 years respectively. The patients were further divided into those below 18 years and those of or above 18 years with 11 patients falling in the former group and 15 patients falling in the latter. Out of 26 patients, liver involvement was the sole presentation in 7 patients, out of which 5 patients were under 18 years and 2 patients were 18 and above, 8 patients had exclusively neurological involvement, out of which 2 patients were under 18 years and 6 patients were 18 and above,3 patients

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had psychiatric manifestations, and all of them were 18 and above, 5 patients had mixed presentation (hepatic, neurological and psychiatric) out of which 1 patient was below 18 years and 4 patients were 18 and above and 3 others were diagnosed after screening tests were performed and all the patients were under 18 years.

Patients who had abdominal manifestations, abdominal pain, jaundice, splenomegaly, ascites and hepatomegaly were the predominant signs while upper gastrointestinal bleeding and encephalopathy were the least frequent. In patients with neurological manifestations, the most prevalent symptom was dysarthria, ataxic gait, dystonia and tremors, and the least common being seizure. In patients with psychiatric manifestations, depression, declining school performance, personality changes and irritability were noted. Patients diagnosed by family screening were asymptomatic at the time of diagnosis.

The clinical features at the time of diagnosis are summarized in table 2.

Out of 7 patients with liver involvement and 5 patients with mixed presentation, chronic liver disease was diagnosed in 9 patients of which 4 patients were under 18 years and 5 patients were above 18 years and 2 patients had acute hepatitis, who were under 18 years and 1 patient had chronic hepatitis who was under 18 years of age.

Kayser-Fleischer rings were noted in 14 (53%) patients out of 26 patients. These rings were most prevalent in 7 patients with exclusive neurological manifestations followed by 4 patients with mixed disease presentation and 3 patients with exclusively hepatic symptoms.

Serum ceruloplasmin levels ranged from 3.1 to 60.1 mg/dl and 22 (84%) out of 26 patients had serum ceruloplasmin levels < 20 mg/dl. 24 hour urinary copper (>100 µg/day) was increased in 17 (65%) patients with 24 hour urinary copper values varying from 26.16 µg/day to 2445.68 µg/day. Serum copper was low (<70mg/dl) in 23 (88%) patients with serum copper values ranging from 13.1mg/dl to 129.4mg/dl.

All 26 patients were submitted to an abdominal ultrasound. Chronic liver disease features were detected in 9 patients, 5 out of 7patients who presented with hepatic symptoms had CLD features, and 4 out of 5 patients with mixed presentation had CLD features. Among the 9 patients with ultrasound abnormalities, portal hypertension was demonstrated in 5 patients.

MRI (magnetic resonance imaging) or CT (computed tomographic) was ordered only in 8 neurological, 3 psychiatric and 5 mixed presentations patients. 8 patients had basal ganglia hyperintensity on T2-weighted MRI images, 2 patients showed hyperintensities in the brainstem, 2 patients showed involvement of thalamus and 1 patient had simultaneous involvement of the basal ganglia, thalamus, and brainstem.

The patients were treated with daily dose of 1-2 g of D-penicillamine. 4 patients had worsening of symptoms, skin rash was noted in 3 cases, gastrointestinal intolerance was was observed in 1 patient and 2 patients developed thrombocytopenia. In these cases the drug was substituted with zinc sulphate (150-250 mg/day).

Out of 26 patients 2 patients with mixed presentations and 1 patient with hepatic manifestations died.

Discussion

Wilson disease is due to a genetic abnormality inherited in an autosomal recessive manner that leads to impairment of cellular copper transport. The majority of patients with Wilson disease are diagnosed between the ages of 5 and 35 years, though this disease has been diagnosed in younger patients and in patients in their 70s (9,10,11-16). The variability in the age of onset of Wilson disease probably reflects differences in mutations and penetrance, extragenic factors, and environmental influences including diet (17). In this study the lowest and the highest age for appearance of this disease was 6 and 53 years respectively. A predominance of women (14 patients) in our study was noted. A gender difference with predominance of women has been documented previously in an Austrian cohort with Wilson disease (18,19,20).

The clinical manifestations of Wilson disease are predominantly hepatic, neurologic, and psychiatric, with many patients having a combination of symptoms (9). In our study out of 26 patients 8 patients had neurologic manifestations, 7 patients had liver involvement, 3 patients had psychiatric manifestations and 5 patients had mixed presentation.

Usually, hepatic disease occurs between the first and second decades of life, whereas neurological symptoms develop later (5,11,21,22,23,24). Our study showed liver involvement in 7 patients out of which 5 patients were under 18 years of age and 2 patients were 18 and above. Neurological manifestations were noted in 6 patients who were18 and above and in 2 patients were below18 years.

The liver is the initial site of copper accumulation in patients with Wilson disease, and there are several different clinical manifestations of hepatic copper accumulation (25,26). Our study showed liver manifestations ranging from chronic hepatitis, to acute hepatitis to cirrhosis. Patients with Wilson disease, most often children or young adults, may develop acute hepatitis (9).In this study acute hepatitis was observed in 2 patients who were under 18 years o age. Chronic hepatitis due to Wilson disease are often asymptomatic from their liver disease. Such patients are diagnosed through family screening. Our study showed that 1 patient had chronic hepatitis who was asymptomatic. Cirrhosis is present at the time of diagnosis of Wilson disease in approximately 35 to 45% of patients overall (24,27,28), including those presenting with neuropsychiatric symptoms or who are asymptomatic (23,28,30,31).In this study it was observed that out of 26 patients 9 (34%) patients had cirrhosis, out of these 9 patients, 5 out of 7 patients who presented with hepatic symptoms had CLD features, and 4 out of 5 patients with mixed presentation had CLD features.

The neurological symptoms of Wilson disease are broad and some of the common manifestations include, dysarthria, gait abnormalities/ataxia, dystonia, tremors, parkinsonism, drooling and seizures are rarely the presenting features. In our study, the most prevalent symptom was dysarthria, ataxic gait, dystonia and tremors, and the least common being seizure.

Behavioural and psychiatric manifestations of Wilson disease include, depression, personality changes, irritability, impulsiveness, declining school performance, inappropriate behaviour (21,32). In this study depression, declining school performance, personality changes and irritability were noted.

Kayser-Fleischer rings are a characteristic feature of Wilson disease and are seen in approximately 90% of patients with neurological manifestations and about 50 to 60% of patients with hepatic manifestations (10,26,33,34,35,36) In this study Kayser-Fleischer rings were noted in 14 (53%) patients out of 26 patients. These rings were most prevalent in 7 (87%) patients out of 8 patients with exclusive neurological manifestations followed by 4 (80%) patients out of 5 patients with mixed disease presentation and 3 (42%) patients out of 7 patients with exclusively hepatic symptoms.

Most of the studies have shown normal blood serum ceruloplasmin levels in only 5% of patients (37). Similarly, in this study only 4 (15%) patients out of 26 patients had normal serum ceruloplasmin levels. Urinary copper excretion is useful for the diagnosis of Wilson disease and for monitoring therapy. Wilson disease is typically associated with 24-hour copper

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excretion of >100 mcg, although lower values have been described in up to 25% of asymptomatic patients with confirmed disease and values >40 mcg/day are suggestive of Wilson disease and warrants further investigations (37,34,36). In this study it was observed that 24 hour urinary copper (>100 µg/day) was increased in 17 (65%) patients and 5 (19%) patients had values between 60 to 100 mcg/day. In Wilson disease, the serum copper concentration is decreased in proportion to the reduction in serum ceruloplasmin, despite the presence of copper overload. Serum copper was low (<70mg/dl) in 23 (88%) patients in this study.

MRI(magnetic resonance imaging) or CT (computed tomographic) scanning of the brain may reveal structural abnormalities in the basal ganglia in patients with neurologic Wilson disease (38). Simultaneous involvement of the basal ganglia, thalamus, and brainstem is highly suggestive of Wilson disease.(39). In this study it was observed that out of 16 patients in whom MRI was ordered 8 patients had involvement of basal ganglia, 2 each showed involvement of thalamus and brainstem and 1 patient had hyperintensities in the basal ganglia, thalamus and brainstem.

Penicillamine is the most commonly used de-coppering drug in India. Use of this drug has been reported to cause worsening of symptoms (40). In this study 4 patients showed worsening of symptoms after the initiation of penicillamine. In these cases the drug was substituted with zinc sulphate (150-250 mg/day). Zinc therapy in India is gaining significant value because of economical reasons and encouraging results in the recent literature. Zinc is cheap, easily available and therefore patients have better compliance and zinc can be used as an effective status while on zinc therapy in Indian population. (41)

Conclusion

Wilsons disease is not that rare in India and has varied clinical presentations. Clinical and biochemical analysis in cases of patients with high degree of suspicion can lead to early treatment with good outcome. Screening of all asymptomatic siblings for Wilson disease is a very important issue and must be carried out in all. Treatment should be individualized, and careful follow-up is mandatory.

Patients characteristics – Table 1

	Age yrs/ Gender	System involvement	KF ring	Serum ceruloplasmin mg/dl (20-60)	Urinary copper excretion µg/day (15-60)	Serum copper mg/dl (70-140)
1	9/M	Asymptomatic		13.6	380.16	34.6
2	23/M	Neurological	+	9.82	88.4	13.1
3	14/F	Neurological	+	16.5	643.0	65.2
4	7/M	Asymptomatic		11	1232.0	129.4
5	12/F	Hepatic disease	+	5.91	584	17.4
6	19/M	Psychiatric disease		18.8	56.20	51.2
7	6/M	Asymptomatic		12.6	121	48.5
8	35/F	Neurological	+	7.7	69.3	20.3
9	23/F	Psychiatric disease		60.1	224.13	24.5
10	10/F	Hepatic disease		16.3	198.0	21.5
11	41/M	Mixed		16.93	97.4	17.8
12	26/F	Psychiatric disease		19.5	433.7	78.2
13	33/F	Neurological	+	34.7	134.9	27.7
14	12/M	Hepatic disease		41.7	289.1	51.1
15	27/M	Hepatic	+	16.3	26.16	31.6
16	11/F	Hepatic disease		3.1	189.9	26.1
17	39/M	Mixed	+	11.5	58.9	42.3
18	16/F	Neurological		14.22	187.3	19.5
19	28/F	Neurological	+	17.75	511.7	97
20	39/M	Neurological	+	14.9	63.0	33
21	8/F	Hepatic disease		18.2	89.9	45.2
22	21/M	Mixed	+	10.5	2445.68	20.3
23	53/M	Mixed	+	28.6	197.0	34.7
24	27/F	Neurological	+	11.1	164.7	66.2
25	26/F	Hepatic	+	17.8	51.8	53
26	13/F	Mixed presentation (liver, neurological &psychiatry)	+	6.91	222.2	60.9

Clinical manifestations – Table 2

Abdominal manifestations	Neurological manifestations	Psychiatric manifestations
Jaundice 11	Dysarthria 10	Depression 8
Abdominal pain 8	Ataxic gait 8	Personality changes 6
Splenomegaly 9	Dystonia 8	Declining school performance 5
Ascites 9	Tremors 6	Irritability 5
Hepatomegaly 3	Seizures 1	
Esophageal varices 3		
Encephalopathy 1		
UGI bleed 1		

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