NEUROLOGICAL AND NEUROPSYCHIATRIC SPECTRUM OF WILSON'S DISEASE IN LOCAL POPULATION

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ABSTRACT

This prospective observational study was conducted in the department of Neurology, King Edward Medical University / Mayo Hospital, Lahore over a period of six months from July to December 2007. The objective was to study the clinical and laboratory features of Wilson Disease in local population and compare the results with national and International data. All consecutive patients who presented with Wilson's disease during this period were included in the study. Their clinical and laboratory features were recorded and compared with the available National and International data. We collected a total of 10 patients from 5 different families. Eight were confirmed cases examined and investigated by the authors. Two cases were probable and dead siblings of these families in whom clinical features strongly supported the diagnosis of Wilson's disease. Clinical and laboratory data of only confirmed cases was tabulated and compared. Of the eight patients six were males and two females with a male to female ratio of 3:1. Mean age at presentation was 12.6 years with a range of 6 to 19 years. Presenting features were as follows: dysarthria in 6 (75%); dystonia 5 (63%); extrapyramidal rigidity and bradykinesia 4 (50%); emotional lability 6(75%); cognitive decline 2 (25%) and signs of chronic liver disease in 1 (13%). Hepatic functions were abnormal in 1 (13%) while 4 (50%) patients had coarse echo texture of liver on abdominal ultrasound. Serum copper levels were within normal range in 8 (100%) patients. Serum ceruloplasmin was low in 8 (100%) patients. Twenty four hour urinary copper excretion was elevated in 5 (63%), KF ring on slit lamp examination was positive in 8 (100%) patients. CT scan of brain was done in 6 (75%) and showed hypodensity of basal ganglia mainly affecting the putamen and globus pallidus along with subcortical white matter disease in fronto-parietal region in 4 (50%) patients. MRI was done in 5 (63%) patients and showed evidence of cortical atrophy with hyperintense signals in thalami, brain stem and basal ganglia in all five patients (100%). Six confirmed cases belonged to three families and no family history was available in two cases (25%). History of consanguineous marriage was positive in all (100%) cases. We conclude that Wilson's disease is not an uncommon problem in our population with patients presenting at an early age but with advanced stage of the disease. However, poor recognition is the possible cause of it's under and delayed diagnosis. Wilson's disease in children and young adults can present with neuropsychiatric features alone without any hepatic manifestations. Neuropsychiatric features along with KF ring and a low Serum Ceruloplasmin level are sufficient to establish a diagnosis of Wilson's disease.

INTRODUCTION

Wilson disease (W.D.), or hepatolenticular degeneration, is a neurodegenerative disease of copper metabolism. It is an autosomal recessive disorder. In 1912, Samuel Kinnier Wilson first described it as a familial disorder associated with neurological symptoms and cirrhosis.[1] Wilson's disease is due to impairment in the ability of liver to incorporate copper into hepatic ceruloplasmin and to export copper from the liver into bile. This is due to the defective transport of copper by the copper-transporting P-type ATPase secondary to one of several mutations in the *ATP7B* gene. By genetic linkage studies, Bowcock and colleagues narrowed the assignment of the Wilson disease locus to 13q14-q21.[2] As a result copper accumulates in the liver, brain, kidney, and cornea.

According to the literature, patients with Wilson disease usually present with liver disease during the first decade of life or with neuropsychiatric illness during the the second or third decade.[3] In general, the younger the age of the patient at symptom onset, the greater is the degree of liver involvement.[4] The incidence rate is 10-30 per million cases, with increased rates in areas of consanguinity. The frequency ranges worldwide from 1 case per 30,000 population in Japan to 1 case per 100,000 population in Australia.

WD is biochemically characterized by low ceruloplasmin and serum copper levels, increased 24-

hour urinary copper excretion, and abnormally high hepatic copper content.[5] Diagnosis of Wilson's disease is based on clinical symptoms and certain laboratory investigations (Leipzig's criteria).[6]

We undertook this study to observe the clinical features especially neurological and neuropsychiatric along with laboratory features of the disease in local population and to compare them with other studies.

METHODS

This is a prospective observational study. It comprises of consecutive cases of Wilson disease diagnosed in Neurology Department Mayo Hospital, Lahore, during a period of six months from July 2007 to December 2007. Diagnosis was based on Leipzig's Criteria.[6] Scoring ranges from 0 to 4; a score of 4 = definitive WD; a score of 2–3 = likely WD; and a score of 0–1 = improbable WD. Patient and all siblings were screened and those fulfilling the criteria were included in the study. History and laboratory record (if any) of siblings who died were reviewed and mentioned in the results of the study as probable cases. Data collected from the case series was recorded on a proforma that included the following five sections: a) demographic details including name, age, and sex ;b) presenting clinical features; c) family history including history of consanguineous marriages; d) laboratory features including serum copper & ceruloplasmin levels, 24 hour urinary copper estimation, liver functions (LFTs), KF ring on slit lamp examination and abdominal ultrasound for liver and spleen; e) radiological features on CT Scan and / or MRI of brain.

RESULTS

We collected 8 confirmed and two probable cases from 5 different families. Of the eight patients six were male and two female with a male to female ratio of 3:1. Mean age was 12.6 years with a range of 6 to 19 years. Presenting features were as follows: dysarthria in 6 (75%); dystonia in 5 (63%); extrapyramidal rigidity and bradykinesia 4 (50%); emotional lability 6 (75%); cognitive decline 2 (25%) and signs of chronic liver disease in 1 (13%). LFT's were abnormal in 1 (13%) while 4 (50%) had coarse echo texture of liver on abdominal ultrasound. Serum copper levels were within normal range in 8 (100%) patients, whereas serum ceruloplasmin was low in 8 (100%) patients. Twenty four hour urinary copper excretion was elevated in 5 (63%), KF ring on slit lamp examination was positive in 8 (100%) patients. CT scan of brain was done in 6 (75%) and showed hypodensity of basal ganglia mainly affecting the putamen and globus pallidus along with subcortical white matter disease in fronto-parietal region in 4 (50%) patients. MRI was performed in 5 (63%) patients and showed evidence of cortical atrophy with hyperintense signals in thalami, brain stem and basal ganglia in all the five patients (100%). Six confirmed cases belonged to three families and no family history was available in two cases (25%). History of consanguineous marriage was positive in all (100%) cases. Clinical and laboratory features are shown in Table 1 and 2.

DISCUSSION

This study revealed that most (n = 75%) of the patients presented in second decade while only 2 (25%) were below 10 years of age. We also observed a male preponderance in our study with male to female ratio of 3:1. This observation is in accordance with the data from the reports in which the age at presentation was 8 to 16 years with male preponderance.[7] Athough, it has been reported as late as 72 years of age,[8] the majority of patients become symptomatic before the age of 50.[9] In the Indian subcontinent, the disorder tends to manifest one decade earlier, which is possibly related to the traditional practice of cooking and eating food using copper utensils.[10]

About 40-50% of patients present with liver disease, and 35-50%, with neurological or psychiatric symptoms.[7] In our study neuropsychiatric disturbances were most common initial manifestations and were seen in 6 (75%) patients. This may be due to the fact that study was conducted in neurology department where patients with neurological manifestations are brought. However, even on detailed analysis of other family members, we observed more neuropsychiatric manifestations than hepatic manifestations. We had only one patient who presented with symptoms of jaundice at the age of 6 year. Wilson's disease with hepatic involvement is usually present in first decade of life. One patient (case 4) had only psychiatric symptoms at presentation with excessively labile mood along with isolated dysarthria as the only neurological feature. He was evaluated on lines of Wilson's disease because of high clinical suspicion and a strongly positive family history. A previous study describes four distinct diagnostic categories based on patients' major neurological findings: 1) **Parkinsonian group** distinguished by the paucity of expression and movement; 2) **Pseudosclerotic group** had tremour resembling multiple sclerosis; 3) **Dystonic group** characterized by hypertonicity associated with abnormal limb movements; and 4) **Choreic group** characterised by choreoathetoid movements associated with dystonia.[11] There may be significant over-lap between these

Table 1: *Clinical & Laboratory features in eight cases investigated for Wilson's disease.*

Clinical features	Case1	Case2	Case3	Case4	Case5	Case6	Case7	Case 8
Age in yrs	19	14	12	13	14	15	8	6
Sex	Male	Female	Female	Male	Male	Male	Male	Male
Dysarthria	Present	Present	Present	Present	Present	Present	Absent	Absent
Dystonia	Present	Present	Present	Absent	Present	Present	Absent	Absent
Extrapyramidal rigidity	Present	Present	Present	Absent	Absent	Present	Absent	Absent
Psychiatric symptoms	Present	Present	Present	Present	Present	Present	Absent	Absent
Cognitive decline	Present	Present	Absent	Absent	Absent	Absent	Absent	Absent
Hepatic involvement	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Present
Family history	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve
24 hour urinary copper mcg/dl	1425	357.91	79	79	339	100.2	211	40
Serum cerulo-plasmin mg/dl	3	2	3	2	3	4	2	7
Serum copper mcg/dl	52.8	54.51	35.73	88	37.95	40.3	45.6	82.3
K-F ring	Present	Present	Present	Present	Present	Present	Present	Present
CT scan:								
a) Hypodense basal ganglia	Present	Present	Normal	Present	Present	Not done	Not done	Normal
b) Subcotical white matter disease	Present	Present		Present	Present			
MRI findings:								
Hyperintense signals in putamen and globus pallidus	Present	Present	Not done	Present	Present	Present	Not done	Not done
Thalami	Present	Present		Present	Present	Present		
Midbrain	Present	Present		Present	Present	Present		
Pons	Present	Present		Present	Present	Present		
Medulla	Present	Present		Present	Present	Present		
Subcortical involvement	Fronto-parietal	Fronto-parietal		None	Fronto-parietal	None		
Ventricular system	Mildly dilated cisterns	Mildly dilated		Normal	Normal	Normal		
cerebellum	Normal	Normal		Normal	Normal	Normal		

groups. Psychiatric manifestations can be divided into affective, behavioral, schizophrenia like and cognitive. Cases in our study had all of the above neurological manifestations except chorea (Table 1). Cognitive decline was seen in 2(25%) patients.

Kayser-Fleischer rings were found in all patients (100%) in our study. Kayser-Fleischer rings have been reported to be present in 95% of patients with neurological symptoms, in 50-60% of patients without neurological symptoms and in

Table 2: *Analysis of families with confirmed and suspected cases of Wilson disease.*

Family no	Family 1	Family 2	Family 3	Family 4	Family 5
Total no of siblings	7	2	4	7	3
Confirmed cases	**2** Case 1 & 4	**2** Case 2 & 8	**2** Case 3 & 7	**1** Case 5	**1** Case 6
Probable cases (dead siblings with similar clinical features)	0	0	**2**	0	0
History of consanguineous marriage	+	+	+	+	+

only 10% of asymptomatic siblings.[12] Patients presenting with neurological symptoms may also suffer from significant liver disease. In a substantial proportion, symptomatic liver disease pre-dates the occurrence of neurological signs.[13] We found that 50% of our patients had evidence of coarse texture of liver but only one patient (13%) had jaundice and raised liver enzymes consistent with chronic liver disease. Seven (87%) cases presented mainly with neurological and neuropsychiatric features but with biochemically normal liver function tests. Liver biopsy and histochemical examination was beyond the scope of this study. Hence we observed that it is not mandatory that all patients with neurological manifestations are likely to have clear cut hepatic impairments. According to previous reports, if a liver biopsy is performed in all patients presenting with neurological symptoms at diagnosis, the proportion of patients with cirrhosis is 38.7% and about one-half of patients have only minimal liver disease.[14]

Leipzig Diagnostic Criteria used for the diagnosis of Wilson disease in this study was proposed in Leipzig Germany 2001 at the 8th international meeting which recommends the presence of KF rings, low serum ceruloplasmin and high 24 hour urinary copper excretion in patients with neurological symptoms for diagnosis of Wilson's disease. Standard criteria for asymptomatic patients is liver biopsy showing copper deposition of greater than 250g/g dry weight in hepatic tissue along with low serum ceruloplasmin.[5] In previous studies serum ceruloplasmin were shown to be a more sensitive indicator for the diagnosis as compared to 24 hour urinary copper levels. We found that 100% cases in our study had low serum ceruloplasmin level and 24 hour urinary copper excretion was elevated in 5 (63%) cases. This supports the previous finding that a low serum ceruloplasmin level is more sensitive marker than serum copper and 24 hour urinary copper excretion in diagnosing Wilson disease.

CT scan and MRI were performed and revealed hypo dense areas in the basal ganglia on CT scan with sub cortical white matter changes mostly in the fronto-parietal regions of the brain. MRI findings were similar to the classical findings described in literature with hyper intense signals on T2 weighted images from the thalami, globus pallidus, putamen, and the brainstem.[15,16] Mild dilatation of the ventricular system was seen in two cases and no cerebellar involvement was observed.

A positive family history was extremely significant in our study and was positive in 75% cases. Two patients had no family history (table 2). Two siblings of case 3 had died undiagnosed. However, history given by the parents regarding their illness strongly suggested the diagnosis of Wilson's disease as the most probable cause of death. They were seen by local physicians and never referred to any tertiary care center. History of consanguineous marriage was present in all cases (100%).

- We **conclude** that Wilson's disease is not uncommon in our local population and most patients present with neurological or neuropsychiatric features at a relatively early age with a male preponderance and with advanced stage of the disease.
- Possibly poor recognition is the cause of it's under and delayed diagnosis.
- Wilson's disease can present in children with isolated neuropsychiatric features without any hepatic manifestation.
- KF rings along with neuropsychiatric features and a low ceruloplasmin level are sufficient to establish a diagnosis of Wilson's disease.
- Low Serum Ceruloplasmin (< 20 mg/dl) is more reliable in supporting the diagnosis of Wilson's disease than 24 hour urinary copper excretion and low serum copper levels.
- All young patients, below the age of 40 years, presenting with neurological or psychiatric features as initial manifestations should be thoroughly screened for Wilson's disease.

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