NEUROLOGICAL MANIFESTATIONS OF WILSON'S DISEASE

Adnan Khan, Azmatullah Khattak, Akhtar Sherin, M Asghar Khalil

Department of Neurology, Postgraduate Medical Institue, Lady Reading Hospital, Peshawar

ABSTRACT

Objectives: To study the frequency of various neurological manifestations in patients with Wilson's Disease.

Material and Methods: Patients suspected of having Wilson's disease were admitted to the Neurology unit of Postgraduate Medical Institute, Lady Reading hospital, Peshawar, for a full work up for Wilson's disease. Only those patients who had neurological signs or symptoms of Wilson's disease were included in this study.

Results: Out of 15 patients 9 were female and 6 were male, ranging in age from 8 to 26 years, with mean age of 15.6 years (SD +/- 5.82). Most common neurological features were tremors followed by rigidity, dysphagia/drooling, speech or gait problems. All patients had low serum ceruloplasmin level and Kayser-Fleischer corneal rings. Liver involvement in the form of cirrhosis was found in 13 (86.7%) patients on ultrasonography, since no liver biopsy was done it could not be determined whether the remaining two patients had liver involvement or not.

Conclusions: Neurological manifestations are not uncommon in Wilson's disease. It should be considered in patients of any age presenting with unusual liver, neurologic or psychiatric abnormalities. It should especially be looked for in children and other young patients with extrapyramidal signs or symptoms.

Key words: Wilson's disease, Neurological manifestations.

INTRODUCTION

Wilson's disease is an autosomal recessive disorder of copper metabolism in individuals with two mutant ATP7B genes. The gene for Wilson's disease has been linked to the long arm of chromosome 13 near the D locus.[1] It has a prevalence of 1in

30,000.[2] Impairment of normal excretion of hepatic copper results in toxic accumulation of metal in liver, brain, and other organs. In general one-third of patients with Wilson's disease have liver disease, one-third have neurologic impairment and one-third have both.[3] Since Wilson's disease can present with a wide array of clinical manifestations, it can lead to serious under diagnosis and thus a great risk of irreversible damage to the brain, liver and other organs. On the other hand appropriate and early medical treatment can prevent further organ damage and reduce the risk of permanent damage.[4] Since not much work has been done on Wilson's disease in Pakistan this study was conducted (and is being continued) to look at the various neurological manifestations of Wilson's disease.

MATERIAL AND METHODS

Patients suspected of having Wilson's disease were admitted to the Neurology unit of Postgraduate Medical Institute, Lady Reading hospital, Peshawar for a full work up for Wilson's disease. Only those patients who had neurological signs or symptoms of Wilson's disease were included in this study. Patient's siblings who were found to have Wilson's disease on screening but no neurological features were excluded from this study. The total number of patients who are being treated for Wilson's disease is 27; the ones with neurological manifestations are 15. In all patients full blood count, ESR, liver function tests, urine routine examination, and serum ceruloplasmin were performed. In all patients abdominal ultrasound was performed and an Ophthalmologist sought. Where appropriate and if the patient could afford other relevant investigations were performed, such as, serum copper, 24 hours urinary copper, CT brain. Liver biopsy was not done in any patient, as we do not have the facilities to measure the liver copper content.

RESULTS

Age distribution ranged between 8-26 years, however, the mean age at presentation to the neurology unit was 15.6 with a SD (+/-) of 4.82. Majority of the patients were between 12 to 16 year's i.e. 73.3%. Nine patients were female and six were males, table 1, although being autosomal recessive disorder it had no bearing on the study but there was females predominance. The presenting features in all these patients were neurological. Table 2 shows the presenting features in descending order of frequency. As can be seen the most common sign was tremor (86.7%), followed by rigidity (80%), drooling/dysphagia (66.7%), dystonia (46.7%), dysarthria (46.7), fixed facial expression (40%), anarthria (33.3%), chorea (33.3%), seizures (33.3%). Bed-ridden patients were 33.3 %, while 3 (60%) of these patients had flexed posturing secondary to contractures. Patients with associated psychiatric features were only 2 (13.3%). On slit lamp examination all patients had Kayser-Fleischer rings (table 3). Clinically hepatomegly was present in 8 patients while hepatosplenomegly was present in 4 patients, while on abdominal ultrasound, features suggestive of cirrhosis liver were found in 13 (86.7%) patients (table 4). Past history of jaundice was present in only two patients (13.3%) and these were treated as viral hepatitis (their viral serology for both "B" and "C" hepatitis was negative). Serum ceruloplasmin was low in all our patients, while full blood count, ESR, liver function tests and urine routine examination were normal in all patients (table 4). Only one

MALE TO FEMALE RATIO

Sex	Frequency	Percentage
MALE	6	40
FEMALE	9	60
TOTAL	15	100

TABLE 1

NEUROLOGICAL FEATURES OF WILSON'S DISEASE

FEATURES	YES		NO	
	N	% age	N	% age
Remors	13	86.7	1	6.7
Rigidity	12	80	2	13.3
Drolling/Dysphagia	10	66.7	5	33.3
Dystonic Posturing	7	46.7	8	53.3
Dysarthria	7	46.7	8	53.3
Fixed Facial Expression	6	40	9	60
Anarthria	5	33.3	10	66.6
Chorea	5	33.3	10	66.6
Seizures	5	33.3	10	66.6
Bedridden	5	33.3	10	66.6
Flexed Posturing	3	20	12	80
Psychiatric Features	2	13.3	13	86.7

TABLE 2

patient had nephrocalcinosis, on abdominal ultrasonography. CT brain was performed in 4 out of 5 patients with seizures, 3 patients had degenerative changes while one patient had a normal scan. Serum copper was done in 3 patients in all of whom it low. Urinary copper was done in 6 patients; all of these patients had high levels.

DISCUSSION

In July 1911 Dr. Samuel AK Wilson (1878-1937) received the gold medal of the University of Edinburgh for a doctoral thesis entitled "Progressive lenticular degeneration: A familial nervous disease associated with cirrhosis of liver". In the following year

CLINICAL SIGNS

CLINICAL SIGNS	PRESENT		ABSENT	
	N	% age	N	% age
KF RINGS	15	100%	0	0
HEPATOMEGLY	8	53.3%	7	46.7%
SPLENOMEGLY	4	26.7%	11	73.3%

TABLE 3

INVESTIGATIONS

	NORMAL		ABNORMAL	
	N	% age	N	% age
FBC	15	100	0	0
ESR	15	100	0	0
LFT's	15	100	0	0
Urine R/e	15	100	0	0
S. Cerulopasmin	0	0	15	100
ABD. U/S	2	13.3	13	86.7

TABLE 4

(1912) Wilson published an article on the same topic in the journal "Brain". Wilson disease is inherited as an autosomal recessive disorder with a worldwide prevalence of 1 in 30,000.[2] Wilson's disease is typically suggested in young patients, ages 5 to 40 years, who have cirrhosis and concurrent neurological and psychiatric disorders, [5] however, it has been diagnosed in patients as old as 58 years of age.+ A gene for Wilson disease has been linked to the long arm of chromosome 13 near the D locus. The heterozygous carrier frequency of 1 in 90 2. Isolation of the Wilson Disease gene (Cu-binding P-type ATPase) was first reported in 1993 by three groups and is a member of a cation-transporting P-type ATPase subfamily.+ The gene is called ATP7B. The Wilson disease gene encodes a cationic transporting P-type ATPase. Expression of this Cu-binding P-type ATPase occurs primarily in the liver, kidney, and placenta.[8] Thomas et al. (1995) reviewed the mutation found in the ATP7B gene. Their findings suggest a wide span in the range of onset of Wilson's disease, perhaps wider then previously considered typical. Mutation that completely disrupts the gene can produce liver disease in early childhood at a time when Wilson's disease is not even considered in the differential diagnosis.[9] The genetic mutation induces extensive changes in copper homeostasis. Normally the amount of copper in the body is kept constant through excretion of

copper from the liver into the bile. In Wilson's disease, the two fundamental defects are reduced biliary transport of copper and an impaired formation of plasma ceruloplasmin. Because ceruloplasmin is present in the liver of the patients with Wilson's disease, a posttranslation defect appears to be responsible for the absence of ceruloplasmin from both bile and serum. The abnormalities in copper metabolism lead to accumulation of metal in the liver and consequently to progressive liver damage. Anatomically, the liver shows focal necrosis that leads to coarsely nodular postnecrotic cirrhosis. Electron microscopic studies have shown that copper is sequestered by lysosomes that become more than normally sensitive to rupture. Copper probably initiates and catalyses oxidation of lysosomal membrane lipids, resulting in lipofuscin accumulation. Subsequently overflow of copper from the liver produces accumulation of in other organs, mainly brain, kidney and cornea.[10]

In general, one third of patients with Wilson's disease have liver disease, one third have neurologic impairment and one third have both.[3] Although Wilson's disease can involve almost any organ, the main organs involved will be discussed briefly.

Wilson's disease has various hepatic presentations. The hepatic disease may be acute, and self limiting mimicking acute hepatitis or may progress rapidly, suggesting fulminant hepatitis or may be more insidious, resembling chronic active hepatitis or cirrhosis of liver with hepatic insufficiency.[11] It should be considered in all cases with unexplained liver disease.[12]

The onset of neurological symptoms is usually in the second and less often in the third decade, rarely beyond that time,[13] however, neurological symptoms have been observed in patients as old as 58 years.[6] Neurological manifestations of Wilson disease include dystonia, tremors of the extremities, choreoathetosis, rigors, dysarthria, and ataxia. Less frequent symptoms include dysphagia, diplopia, nystagmus, and Babinski's sign.[13,14]

The characteristic psychiatric symptoms include incongruous behavior, irritability, depression, and cognitive impairment.[15] Wilson disease may result in dementia if not treated properly.[16] Rarely it may present with mania, psychosis, schizophrenia etc.

The Kayser-Fleischer ring is a deep copper-coloured ring at the periphery of the cornea, which is frequently found in Wilson's disease is usually shown by slit lamp examination but sometimes can be seen with naked eye. It is present in almost all patients with neurological manifestations, its density correlates with the duration of clinical symptoms. The rings have been observed to disappear over a variable period with successful treatment including liver transplantation.[17] Identical pigmented corneal rings have also been reported in non-Wilsonian live disease, such as, primary biliary cirrhosis, progressive intrahepatic cholestasis, chronic active hepatitis and multiple myeloma,[18] however, only in Wilson's disease are subnormal levels of ceruloplasmin present with KF-rings.

The commonest symptom for which our patient's seeked medical advises was tremors, rigidity, speech problems, dysphagia/ drooling or gait abnormalities. Although the mean age at presentation to the neurology unit was 15.6 years it ranged from 8-26 years, all these patients had received treatment for their symptoms but non were diagnosed or treated as Wilson's disease. As the outcome of this disease depends on early diagnosis and appropriate treatment one of the main parameters we wanted to study was the duration from the first symptom to the diagnosis and the response to treatment, but we failed to do so because the patients, as well as their relatives, were very not very sure about the onset of symptoms, so this

aspect of the study was dropped. However, roughly the average delay in the diagnosis was more than 6 months (as recorded from there various prescriptions, it range from 3 to 11 months). One of the main reason for the delay in diagnosis was most of the patients belonged to far flung areas with no access to proper medical facilities and the majority of the patients were treated symptomatically by different GP's.

A study published in Mayo Clinic in January 1979,19 showed the analysis of fifty-eight patients with Wilson's disease, in which 25 symptomatic patients experienced liver disease first and 28 with brain disease. Ten of these patients presented with liver disease alone,[19] with brain disease alone, and 24 with evidence of both liver and brain disease. The remaining 5 were discovered as asymptomatic siblings of known patients. Three of the patients with hepatic presentation and one with neurologic presentation later experienced the other type of symptomatology, bringing the total number of patients with mixed disease to 28. Of the 44 patients with brain disease, 12 (27.3%) presented with extrapyramidal findings, 6 (13.6%) with cerebellar findings and 17 (38.6%) with both. Pseudobulbar findings were noted in 9 (20.5%) patients, all of them had other symptoms of severe nervous system disease. In addition to these presentations, in an appreciable number of patients the first symptoms were of a mental or emotional disorder. Disease of the other organ systems, such as joints or kidneys, also occurred but infrequently. When adequate family information was available, 13 of 65 siblings (20%) were known to have had or were suspected of having had Wilson's disease. This is consistent with the autosomal recessive pattern of inheritance. In our study extrapyramidal findings were present in 93.3%, cerebellar in none, pseudobulbar in 66.7% and as expected with other severe neurological signs and symptoms. In 86.7% of the patients there was evidence of both liver and brain disease, while only 2 patients (13.3%) had history of jaundice in the past, rest of these patients had an asymptomatic liver involvement. Renal involvement in the form of nephrocalcinosis was found in only one patient while no pure joint involvement was observed in any of the patients. Kayser-Fleischer rings as expected were present in all patients.[13] Seizure were present in 33.3% in our study while it is generally reported as 5%,[20] which is much higher then reported in the texts as well as other studies conducted.

The CT and MRI abnormalities, which are due to copper deposition and gliosis, are symmetrical and involve the basal ganglia, thalamus, pons, substantia nigra, peri-aqueductal grey matter, tectum and red nucleus. The lesions are of decreased attenuation on CT and of variable high and low intensity on T2WI on MRI. Most patients show generalised cerebral atrophy and the extent of imaging changes shows a close correlation with the severity of symptoms.[21] In our study CT was performed in only 4 of the 5 patients with seizures, three of the patients showed degenerative changes, the fifth patient could not afford this investigation.

CONCLUSION

Wilson's disease is characterised by neuropsychiatric, liver, eye and other organ system involvement. Since the disease has an insidious evolution and the patient may have multi-system involvement, there is usually a delay in diagnosis resulting in less therapeutic effectiveness. We must suspect this disease especially in children such as deterioration of handwriting, school failures or other features suggestive of extrapyramidal nature. Such patients should be screened for Wilson's disease, especially if they have concomitant hepatic disease. We must not hesitate to consider it even given purely psychiatric features.

REFERENCES

1- Frydman M, Bonne-Tamir B, Farrer LA, et al. Assignment of the gene for Wilson's disease to chromosome 13: linkage to the esterase D locus. Proc Natl Acad Sci USA 1985; 82: 1819.

2- Scheinberg IH. Wilson's disease. Chap345, In. Fauci AS, Braunwald E,Isselbacher KJ, et al {Eds}. Harrison's Principles of Internal Medicine, 14th Edition Volume II; New York, Mc Graw Hill, 1998: 2166.

3- Gall AW. Wilson's disease. Chap 220, In. Goldman L, Bennet JC. Cecil Textbook of Medicine, 21st Edition, Philadelphia; Goldman Bennett-Saunders: 1130.

4- Brewer GJ. Practical recommendations and new therapies for Wilson's disease. Drug 1995; 50:240.

5- Schoen RE, Sternlieb I. Clinical aspects of Wilson's disease. Am J Gastroenterol 1990; 85:1453.

6- Fitzgerald MA, Gross JB, Goldstein NP, Wahner HW, Mc Call JT. Wilson's disease (hepatolenticular degeneration) of late adult onset: report of a case. Mayo Clin. Proc. 1975; 50: 442.

7- Bull E, Tanzi A, Petrukhin P, et al. Nature Genetics 1993; 5: 327.

8- Chelly and Monaco, Nature Genetics 1993; 5: 317.

9- Bull PC, Cox DW. Wilson disease and Menkes disease: new handles on heavy metal transport. Trends Genet 1994; 10: 246.

10- Menkes JH. Disorder of metal metabolism, Merritt's Neurology, Tenth edition, Philadelphia, Lippincott Williams & Wilkins 2000; 543.

11- McCullough AJ et al. Diagnosis of Wilson's disease presenting as fulimanent hepatitis: Gastroentrology 1983; 84: 161.

12- Bellary SV, Shankaran K, Desai HG. Wilson's disease: a diagnosis made in two individuals greater then 40 years of age. J Okla State Med Assoc 1993; 86: 441.

13- Victor, Roppers. The inherited metabolic diseases of nervous system, Adams and Victor's Principles of Neurology, Seventh Edition, Mc Graw Hill, United States of America: 2001; 1026.

14- Topalogulu H, Gucuyener K, Orken C, et al. Tremors of the tongue and dysarthria as the sole manifestation as the sole manifestation of Wilson disease. Clin Neurol Neurosurgery 1990; 92: 295.

15- Dening TR, Berrios GE. Wilson disease: a longitudinal study of Psychiatric problems. Biol Psychiatry 1990; 28: 255.

16- Lang C, Muller D, Claus D, et al. Neuropsychological findings in treated Wilson disease. Acta Neurol Scand 1990; 81: 75.

17- Song HS, Ku WC, Chen CLTI Disappearance of Kayser-Fleischer rings following liver transplantation. Transplant Proc 1992; 24: 1483.

18- Fleming CR, Dickson ER, Wahner HW, et al: Pigmented corneal rings in non-Wilsonian liver diseases. Ann Intern Med 1978; 86: 285.

19- Dobyns, W.B.; Goldstein, N.P.; Gordon, H.: Clinical spectrum of Wilson's disease (hepatolenticular degeneration). Mayo Clin. Proc. 1979; 54: 35.

20- Denning TR, Berrios GE, Walshe JM: Wilson's disease and epilepsy. Brain 1988; 111: 1139.

21- Jackson A Neurodegenerative and white matter disease Chapter 8, In: Gillespie J.E., Jackson A. MRI and CT of the Brain; London, Arnold, 2000: 249.

Address for Correspondence:
Dr Adnan Khan,
Senior Registrar,
Neurology Unit,
PGMI/LRH, Peshawar.
E-mail: dradnankhan1961@yahoo.com