Original Research Paper

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Neurology

DIFFERENT PRESENTATIONS OF WILSON DISEASE IN A TERTIARY CARE CENTRE IN SOUTH TAMIL NADU

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ABSTRACT Wilson disease is an autosomal recessive disorder of copper metabolism. Diagnosis depends primarily on clinical features, biochemical parameters and the presence of the Kayser-Fleischer ring. Genetic analysis for mutations within ATP7B is a convincing diagnostic tool. The traditional treatment for WD includes chelation of excessive copper accumulation and reduction of copper intake. Medical therapy is effective but WD is not yet curable. Liver transplantation is especially helpful for patients who fail to respond to medical therapy or present with fulminant liver failure, although evaluation of its long-term effect are still in need.

KEYWORDS : Wilson disease, Copper, ATP7B, COMMD1, D-penicillamin, Trientine, Zinc, Ammonium tetrathiomolybdate, Liver transplantation

INTRODUCTION

Copper is an essential metal that is an important cofactor for many proteins. The average diet provides substantial amounts of copper, typically 2-5 mg/day; the recommended intake is 0.9 mg/day. Most dietary copper ends up being excreted. Copper is absorbed by enterocytes mainly in the duodenum and proximal small intestine and transported in the portal circulation in association with albumin and the amino acid histidine to the liver, where it is avidly removed from the circulation. The liver utilizes some copper for metabolic needs, synthesizes and secretes the copper-containing protein ceruloplasmin, and excretes excess copper into bile. Processes that impair biliary copper excretion can lead to increases in hepatic copper content.

Wilson disease (WD; also known as hepatolenticular degeneration) was first described in 1912 by Kinnear Wilson as "progressive lenticular degeneration," a familial, lethal neurological disease accompanied by chronic liver disease leading to cirrhosis.5 Over the next several decades, the role of copper in the pathogenesis of WD was established, and the pattern of inheritance was determined to be autosomal recessive.6,7 In 1993, the abnormal gene in WD was identified.8-10 This gene, ATP7B, encodes a metal-transporting P-type adenosine triphosphatase (ATPase), which is expressed mainly in hepatocytes and functions in the transmembrane transport of copper within hepatocytes. Absent or reduced function of ATP7B protein leads to decreased hepatocellular excretion of copper into bile. This results in hepatic copper accumulation and injury. Eventually, copper is released into the bloodstream and deposited in other organs, notably the brain, kidneys, and cornea. Failure to incorporate copper into ceruloplasmin is an additional consequence of the loss of functional ATP7B protein.

The hepatic production and secretion of the ceruloplasmin protein without copper, apoceruloplasmin, result in the decreased blood level of ceruloplasmin found in most patients withWDdue to the reduced half-life of apoceruloplasmin.

WD presents with liver disease more often in children and younger adult patients than in older adults. Symptoms at any age are frequently nonspecific. Neurologic manifestations of WD typically present later than the liver disease, most often in the third decade of life, but they can present in childhood Earlier subtle findings may appear in pediatric patients, including changes in behavior, deterioration in schoolwork, or inability to perform activities requiring good hand-eye coordination. Handwriting may deteriorate, and cramped small handwriting as in Parkinson disease (micrographia) may develop. Other common findings in those presenting with neurologic disease include tremor, lack of motor coordination, drooling, dysarthria, dystonia, and spasticity. Because of pseudobulbar palsy, transfer dysphagia may also occur, with a risk of aspiration if severe. Dysautonomia may be present. Migraine headaches and insomnia may be reported; however, seizures are infrequent. Along with behavioral changes, other psychiatric manifestations include depression, anxiety, and even frank psychosis. Many of the individuals with neurologic or psychiatric manifestations may have cirrhosis, but frequently they are not symptomatic from their liver disease.

CASE SERIES:

We, from the department of neurology have collected nearly 13 cases of Wilson disease. The diagnosis of each of the case is based on LEIPZIG SCORING SYSTEM 2001.The above data was collected over a period of 1 year from 2014 – 2015. Out of 13 cases , eight cases are male and 5 cases are female. Among the various presentations of Wilson disease in neurology,most of our cases have mixed presentation. Out of the presentations pseudosclerosis(46%) stands the first, followed by akinetic rigid and ataxia presentation,later followed by dystonia.One of our patient has choreoathetosis as presentation.Among the 13 cases all the patient has KF ring(100%). Regarding hepatic involvement,five patients(38%) among the 13 had altered LFT. Three of our patient (23%)had cognitive impairment. With regarding the Leipzig score, all the above patients scored more than four indicating established Wilson disease.

We did not have any psychiatric presentation in our cases nor do asymptomatic cases. Various case reports have been published from india stating from Dastur et al, Singh et al, Raiamani et al and Tay et al etc.. The mean age of onset in the above cases were 13 years. Male cases dominated in the above case reports as ours.Their clinical profile also included hepatic, neurological , hepatic + neurological as in our cases

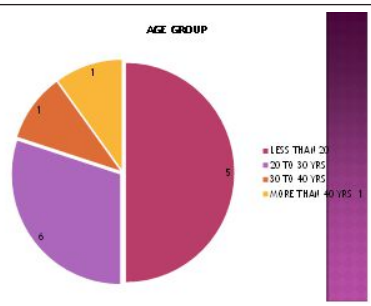
CASE REPORTS FROM DEPARTMENT OF NEUROLOGY, GRH, MADURAI

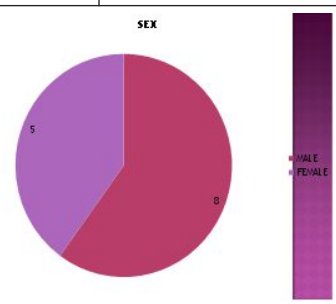
DETAILS	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5	CASE 6	CASE 7	CASE 8	CASE 9	CASE 10	CASE 11	CASE 12	CASE 13	TOTAL
AGE	21	15	15	18	51	13	35	24	15	21	22	23	21	
SEX	M	F	M	M	M	F	F	M	F	M	M	F	M	M-8/F-5
AKINETIC RIGID	-	+	-	-	+	-	-	+	+	+	-	-	-	5
PSEUDOSCLEROSIS (TREMOR)	+	-	-	-	-	-	+	+	-	+	+	+	-	6
ATAXIA	+	-	-	-	-	-	+	-	-	-	+	+	+	5
DYSTONIA	-	+	+	-	-	+	-	-	+	-	-	-	-	4

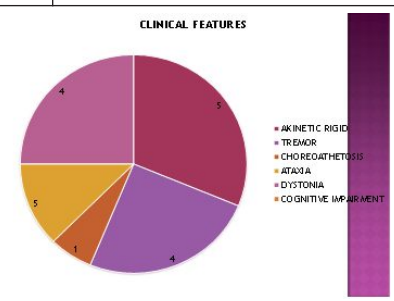
OTHERS	-	-	-	**CHOREO ATHETOS IS**	-	-	-	-	-	-	-	-	-	1
HEPATIC INV.	-	+	-	+	-	-	-	-	-	-	+	+	+	5
COGNITIVE IMPAIRMENT	-	+	-	+	-	-	-	-	-	+	-	-	-	3
KF RING	+	+	+	+	+	+	+	+	+	+	+	+	+	13
F/H	+	-	-	+	-	-	-	-	-	+	-	-	-	2
MRI FINDINGS	+	+	+	+	+	+	+	+	+	+	+	+	+	13
LEIPZIG SCORE	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	>4	13

LEIPZIG SCORING SYSTEM- 2001

CLINICAL SYMPTOMS AND SIGNS		SCORE
KF RING	PRESENT	2
	ABSENT	0
NEUROLOGIC SYMPTOMS	SEVERE	2
	MILD	1
	ABSENT	0
SERUM CERULOPLASMIN	NORMAL(>0.2g/L)	2
	0.1-0.2g/L	1
	<0.1g/L	0
COOMBS NEGATIVE HEMOLYTIC ANAEMIA	PRESENT	1
	ABSENT	0
LIVER COPPER(IN THE ABSENCE OF CHOLESTASIS)	>5* ULN(>4micromol/g)	2
	0.8-4	1
	<0.8	-1
RHODANINE POSITIVE GRANULES		1
URINARY COPPER (IN THE ABSENCE OF ACUTE HEPATITIS)	NORMAL	0
	1-2 ULN	1
	>2 ULN	2
	NORMAL, BUT > 5 ULN AFTER D-PENICILLAMINE	2
MUTATION ANALYSIS	BOTH CHROMOSOMES DETECTED	4
	ON 1 CHROMOSOME DETECTED	1
	NO MUTATION	0
TOTAL SCORE		>=4- DIAGNOSIS ESTABLISHED 3 DIAGNOSIS POSSIBLE, MORE TEST NEEDED <= 2DIAGNOSIS UNLIKELEY







CLINCAL CHARACTERISTICS OF WILSON DISEASE PATIENTS IN VARIOUS INDIAN STUDIES INCLUDING OUR STUDY

GROUP	Dastur et al	Singh et al	Raiamani et al	Murthy et al	Pandit et al	Jha et al	Sinha et al	Taly et al	GRH, Madurai
year	1968	1978	1987	1988	2002	1998	2001	2007	2015
Study period	1959-68	1972-75	1968-1986	1979-1986	1980-2000	1984-93	1991-2000	1970-200-	2014-2015
Place of study	bombay	pondicherry	vellore	Hyderabad	pune	New delhi	ranchi	bangalore	Madurai
No of cases	23	08	30	12	124	22	49	282	13
M:F	15:8	5:3	22:08	11:1		20:2	38:11	196:86	8:5
Clinical pattern									

1)Hepatic	1	3	11	1	67	-	-	42	-
2)Neurologic	10	3	13	10	28	-	34	-	8
3)Hepatic + neurologic	2	0	-	1	0	-	15	10	5
4)Psychiatric	-	-	-	-	-	-	-	7	-
5)Others	5	-	-	-	10	-	-	-	-

We are following up the patient regularly. All of our patient are on treatment with D penicillamine and Zinc . They are symptomatically better. No reported side effects of the drugs .

CONCLUSION

We conclude that Wilson's disease is not uncommon in our population .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.

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 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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