Original Research Article

Study of Pattern of neurological and hepatic manifestation of Wilson's disease

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Abstract

Background: The incidence of Wilson's disease (WD) is 1 in 30,000 individuals. Understanding the neurological and hepatic manifestation can help in early recognition and intervention. **Aims and objective:** To study and compare the pattern of neurological and hepatic manifestation of WD. **Materials and methods:** Fifty patients with WD were studied prospectively at the Medicine Department Gandhi Medical College and Hamidia Hospital, Bhopal, from July 2018 to June 2021. Detailed demographic and clinical history was obtained along with laboratory investigation details such as CBC, platelets, RFT, LFT, RBS, Sr. - Sodium - Potassium, Sr - Calcium - Magnesium, CT/MRI Head and EEG. **Results:** WD was more prevalent in the young and working-age group of 21-30 years (38%). Ascites, abnormal hemoglobin level (98%), SGOT (100%), SGPT (80%), total bilirubin level (72%), AKPo4 (46%), TLC (34%), INR (86%) and 52% had negative K-f ring. Altered echotexture splenomegaly (22%) was the most common finding in USG. The majority of the patients had shown the presence of D-penicillamine/zinc (80%) Consumption. Those with T2 weighted hyperintensity in putamen thalami brainstem c brain atrophy had mean serum ceruloplasmin and a 24-hour urinary copper level of 15.20 and 160.49. In contrast, those with T1 weighted image hypointensity and brain atrophy mean serum ceruloplasmin and a 24-hour urinary copper level of 7.83 and 145.34. **Conclusion:** Patients with WD were young. The presence of ascites, abnormal hemoglobin was common. Abnormality in liver function tests is highly prevalent in WD. Change in the sonographic liver texture and a Kayser-Fleischer ring (KFR) can support the suspicion of the disease. T2 weighted, hyperintensity in putamen thalami brainstem c brain atrophy and T1 weighted image hypointensity and brain atrophy were also common and correlated with the Serum Ceruloplasmin and 24-Hour Urinary Copper level.

Keywords: copper metabolism, incidence, ceruloplasmin protein, neurologic symptoms

Introduction

Wilson disease (WD) is a rare, autosomal, recessive inborn error of the copper metabolism caused by a mutation in the copper transporting gene, ATP7B. The incidence of WD is estimated to be 1 in 30,000 individuals, and the carrier frequency is approximately 1 in 90[1].Copper is an element that is essential for the function of a variety of enzymes that participate in many physiological pathways[2-4]. The hepatic production and the secretion of the ceruloplasmin protein without copper and apoceruloplasmin result in the decreased blood level of ceruloplasmin which is found in most patients with WD[5]. The manifestations are more likely to be hepatic in early childhood and to be neurological in adolescents[6].

The onset of neurologic symptoms is usually in the second and less often in the third decade. The first neurological manifestations are most often extrapyramidal with a propensity to affect the oropharyngeal musculature. The typical presentations are tremors of a limb or the head and generalized slowness of movement or slowness of the tongue, lips, pharynx, larynx, and jaws, resulting in dysarthria, dysphagia, and hoarseness. As the disease progresses, the classic syndrome with features of parkinsonism develops[3].

Newer advances in medicine have brought a considerable degree of relief. The disease can be diagnosed at an early stage, and potential treatment options are available to prevent and reduce the morbidity caused by the neurological disorder.

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Therefore, considerable improvements have to be made to study the disease's epidemiology in our community and develop cost-effective methods to diagnose and provide treatment. Research must be initiated to know the genetics of the Indian Wilson, which present at an earlier age group when compared with the western world.

Given the early occurrence and the multiple modes of presentation, with particular preference to the nervous system, an attempt has been made to pick up Wilson's disease through the nervous system.

Materials and Methods

A prospective observational study was performed on 50 patients at the Medicine Department Gandhi Medical College and Hamidia Hospital, Bhopal, from July 2018 to June 2021. Patients attending the OPD and emergency department with a diagnosis of WD showing hepatic and neurological manifestations in the department of medicine in Hamidia Hospital, Bhopal All patients presenting with Hepatic and neurological manifestations of either sex were included, whereas patients with pseudoseizures/NEAD (Non-Epileptic disorders) were excluded.

All the patients were subjected to CBC, platelets, RFT, LFT, RBS, Sr. - Sodium - Potassium, Sr - Calcium - Magnesium, CT/MRI Head, and EEG.All the data analysis was performed using IBM SPSS ver. 20 software. Frequency distribution and cross-tabulation were used to prepare the tables. Quantitively data were expressed as mean and standard deviation, whereas qualitative data were expressed as numbers and percentages. Comparison of Serum Ceruloplasmin 24 Hour and Urinary Copper with imaging findings were made using one-way ANOVA. A p-value of <0.05 was considered significant.

Results

WD was more prevalent in the young and working-age group of 21-30 years (38%) followed by 31-40 years (30%), whereas 26% of the patients with WD had ages between 11-20.

The majority of the patients with WD had positive ascites. Abnormal hemoglobin level was also more prevalent (98%).

On analyzing the liver function test among the patients with WD, it was found that all the 50 patients had abnormal SGOT, 80% had abnormal SGPT, 72% had abnormal total bilirubin level, and AKPo4 was abnormal in 46% of patients. Out of 50 patients with Wilson's disease, 17 (34%) of the patients had abnormal TLC levels, 86% had abnormal INR levels, 52% had negative K-f ring,

Table 1: Distribution of patients according to USG

USG	Frequency	Percent
Gross ascites altered echotexture liver paranchyma	1	2.0
Altered echotexture mild ascites	10	20.0
Altered echotexture gross ascites splenomegaly	3	6.0
Altered echotexture splenomegaly	11	22.0
Mild ascites	11	22.0
Normal	13	26.0
Mild hepatomegaly altered paranchyma IHBR	1	2.0
Total	50	100.0

A most common finding in USG was altered echotexture splenomegaly (22%) followed by mild ascites (22%), and 20% of the patients with WD had altered echotexture mild ascites. The majority of the patients had shown the presence of D-penicillamine/zinc (80%) Consumption.

Out of 50 patients, 18 (36%) patients had tremors/seizures; half had hepatic encephalopathy, 26% had T2 weighted, hyperintensity in putamen thalami brainstem c, whereas 3 (6%) patients had T1 weighted image hypointensity and brain atrophy.

Table 2: Comparing serum ceruloplasmin and 24 hours urinary copper with imaging findings

Imaging	Serum Ceruloplasmin	24 Hour Urinary Copper
T2 weighted, hyperintensity in putamen thalami brainstem c brain atrophy	15.20 ±13.02	160.49 ±104.46
T1 weighted image hypointensity and brain atrophy	7.83 ±3.76	145.34 ±91.84
Normal	10.52 ±3.58	126.02± 74.10
Not Done	10.52 ±4.15	199.59 ±188.85
Total	11.58 ±7.63	180.28 ±158.45
P-value	0.233	0.750

Those with T2 weighted hyperintensity in putamen thalami brainstem c brain atrophy had mean serum ceruloplasmin and a 24-hour urinary copper level of 15.20 and 160.49. In contrast, those with T1 weighted image hypointensity and brain atrophy mean serum ceruloplasmin and a 24-hour urinary copper level of 7.83 and 145.34, which seems to be lower than those suffering from T2 weighted hyperintensity in putamen thalami brainstem c brain atrophy.

Discussion

WD is an inherited genetic disorder caused by copper metabolism disturbances with main hepatic, neurological, and psychiatric presentation. Deposits of copper accumulate in different organs and may cause a broad range of clinical manifestations. Patients with WD may present with ophthalmological symptoms or renal, cardiac and osteoarticular involvement[3]. In the present study, we tried to study the pattern of neurological and hepatic manifestation of WD.

Clinical features depend on the predominant organ involved (mainly liver and brain), and the disease has been reported from 3 to 85 years of age. Although copper starts accumulating soon after birth, the disease takes at least 3 years to manifest. In the present study, WD was more prevalent in the young and working-age group of 21-30 years (38%) followed by 31-40 years (30%). At the same time, 26% of the patients with WD had an age between 11-20. Symptoms depend on the site of deposition of copper in the body. Walshe and Yeall demonstrated an age-phenotypic presentation. The hepatic presentation was seen in younger age groups (18 years: 24%), while neuropsychiatric manifestation increased as age advanced (18 years: 74%)[7].

Symptom onset to diagnosis was shorter in hepatic (6 months) than neuropsychiatric presentation (18 months). Studies in children from India and Egypt have shown isolated hepatic involvement (20–54%), isolated neurological (8–22%), neurohepatic (11–36%), asymptomatic (15–35%), and other manifestations (0–22%)[6,8,9].

In the present study majority of the patients with WD were found to be positive for ascites. In the present study, abnormal hemoglobin levels showed high prevalence in WD as the majority (98%) had abnormal hemoglobin levels. Previous studies have shown that acute hepatitis in WD occurs in 10–25% of the patients[6,9,10]. Acute liver failure (ALF) (8–20%)22, 28 is predominantly seen in childhood and adolescents[11,12]. However, in the present study, all 50 patients had abnormal SGOT, 80%had abnormal SGPT, 72% had abnormal total bilirubin level, and AKPo4 was abnormal in 46%. The presentation mimics acute hepatitis, but the condition deteriorates rapidly over days to weeks and is often fatal. It results in deep jaundice, hemolysis, coagulopathy, ascites, encephalopathy, and renal failure. In line with the present study, previous investigations showed very high serum bilirubin, the mild-to-moderate rise of liver enzymes, low serum alkaline phosphatase, low serum uric acid, and defective synthetic functions[13,14]. The combination of the ratio of serum alkaline phosphatase/total bilirubin 2.2 has been described to have a diagnostic sensitivity and specificity of 100%. In 2 studies on acute on chronic liver failure (ACLF) (11– 55%)25, 32 from India, WD was the underlying chronic liver disease in 42–43% of patients with a superadded acute viral hepatitis[15,16].Laboratory-chemical involvement of the liver (transaminases, synthesis parameters albumin and coagulation factors, cholinesterase, ammonia), sonographic liver texture changes, and a Kayser-Fleischer ring (KFR) can support the suspicion of the disease[17]. In the present study, the patients with WD majority had negative K-f rings (52%), whereas 48% had shown positive K-f rings. Previous studies have also reported that patients with neurological presentations tend to be older (second/third decade) and usually have a Kayser-Fleischer (KF) ring.

In the present study, the most common finding in USG in patients with WD was altered echotexture splenomegaly (22%) followed by mild ascites (22%), and 20% of the patients with WD had altered echotexture mild ascites. In the present study, out of 50 patients with WD, most of the patients had shown the consumption of D-penicillamine/zinc (80%).

Most patients who present with central nervous system (CNS) manifestations have the liver disease at the time of presentation, though not symptomatic. Contrary to the initial belief that hepatic form is the predominant presentation of WD, over the years, published literature has noted that neurological manifestations tend to be more common at presentation, accounting for as high as 60%. The presenting neurological symptoms tend to be wide and variable. In the present study, out of 50 patients, 18 (36%) patients had tremors/seizures, half of the patients suffered from hepatic encephalopathy (50%), 13 (26%) patients had observed to have T2 weighted hyperintensity in putamen thalami brainstem c brain atrophy whereas 3 (6%) patients had T1 weighted image hypointensity and brain atrophy. In a series of 307 patients from India, the common presenting symptoms were tremors (31.6%), dysarthria (15.6%),

jaundice (12.4%), abnormal gait (8.8%), abdominal distention (7.8%), musculoskeletal symptoms (5.2%), seizures (4.9%), behavioral problems (4.6%), dystonia (3.6%), clumsiness (2.6%), drooling of saliva (2.6%), generalized weakness (2.3%), decreased scholastic performance (1.9%), changed sensorium (1.3%), bleeding symptoms (1.3%), dysphagia (0.9%), chorea (0.3%), and poor vision (0.3%). Throughout the disease, patients tend to develop a varied combination of these presenting features[18].

The Cu pool in the musculoskeletal system is in constant exchange with plasma. Plasma contains approximately 1 mcg/mL, of which 60–95% is bound to ceruloplasmin. Ceruloplasmin is a source of Cu for peripheral organs, where Cu is an essential cofactor for many enzymes[19]. In patients with T2 weighted, hyperintensity in putamen thalami brainstem c brain atrophy, mean serum Ceruloplasmin was 15.20. In contrast, those with T1 weighted image hypointensity and brain atrophy mean Serum Ceruloplasmin was 7.83, which seems to be lower than those suffering from T2 weighted hyperintensity in putamen thalami brainstem c brain atrophy. Normal dietary Cu intake is 1.5–5 mg in 24 h, 50–60% of which is unabsorbed and excreted in feces; 25–40% is absorbed from the duodenum, stored by enterocytes, and bound to metallothioneins in a nontoxic form. From this intestinal pool, 75% flows through the portal system with albumin or transcurrent, and the liver takes up. The remaining 25% is bound to albumin in the circulation. In the liver, 20% of Cu is re-excreted back into the gastrointestinal tract through bile, and 80% is transported to the periphery, bound to ceruloplasmin. Levels of copper in the hepatocytes regulate the intracellular distribution and function of ATP7B. When intracellular copper is in excess, ATP7B facilitates its excretion into bile by exocytosis. Mutations in ATP7B result in decreased synthesis of copper-bound ceruloplasmin, impaired excretion of copper, and increased cytosolic, mitochondrial, and nuclear levels of copper[19].Twenty-four–Hour Urinary Copper Assay This is a sensitive test that indirectly reflects the serum-free copper level. The urine sample must be collected in a copper-free container, and the test should be done before chelators are started. It is an excellent test in symptomatic patients but may be false negative in those who are asymptomatic[20,21]. A level >100 mcg/24-hour is considered virtually diagnostic, but recent studies have shown that lowering the cut-off levels to 40 mcg/24-hour for asymptomatic patients increases the sensitivity[21]. In patients with T2 weighted, hyperintensity in putamen thalami brainstem c brain atrophy, mean 24 Hour Urinary Copper level was 160.49, whereas in those with T1 weighted image hypointensity and brain atrophy 24 Hour Urinary Copper level was 145.34, which seems to be lower than those suffering from T2 weighted hyperintensity in putamen thalami brainstem c brain atrophy. The present study had few limitations; small sample size and lack of randomization were a few. There is a need for a large randomized clinical trial to provide strength to present study findings.

Conclusion

Based on the finding, we can conclude that patients with WD had an age between 11-20. The presence of ascites, abnormal hemoglobin is common. Abnormality in liver function tests is highly prevalent in WD. Change in the sonographic liver texture and a Kayser-Fleischer ring (KFR) can support the suspicion of the disease.

The most common features were tremors/seizures and the presence of hepatic encephalopathy. T2 weighted, hyperintensity in putamen thalami brainstem c brain atrophy and T1 weighted image hypointensity and brain atrophy are also common and correlated with the Serum Ceruloplasmin and 24-Hour Urinary Copper level.

WD is perhaps more common than reported from India. Such epidemiological studies will provide strength to present evidence. A nationwide registry may improve awareness among medical communities and lead to early diagnosis and prompt treatment. Once the diagnosis is established, the patient and the caregiver need to be educated regarding compliance and long-term follow-up.

Conflict of Interest: Nil Source of support: Nil

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