AN ANALYTICAL STUDY REPORT ON WILSON DISEASE
NEURODEGENERATIVE SYNDROME DUE TO COPPER METABOLISM

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Abstract
Wilson’s disease (WD) is defined as neurodegenerative syndrome due to copper metabolism. The psychiatric manifestations of Wilson’s disease include schizophrenia, psychosis, delusions. The persistence of the statement is to exist a short review of Wilson’s disease which was diagnosed along with HP syndrome at Manipal hospital. Due to the lack of recognition about the Wilson’s disease signs and symptoms primes to postponements in treatment and management. The objectives of our case report is to review the wilson disease neurodegenerative syndrome due to copper metabolism.

Keywords: Wilson’s disease, Hepatopulmonary syndrome, copper metabolism

1 Introduction
Wilson’s disease (WD) is an autosomal recessive syndrome of copper metabolism which is important for the buildup of copper metal in various organs and tissues in the body1-2. Dr. Wilson primary designated WD in 12 patients in 1912.3 Prevalence of WD is 1; 30,0004 is produced by alteration of the genetic factor called ATP7B that encrypting a copper conveying P-type ATP as that is essential for copper excretion into bile5. WD is added predominant in fresher population by mean age of 15–20 years and age of performance, and hardly grown-up in 40 years of age6. WD has an extensive range of presentations. Patients’ might exist by main hepatic or neurologic symptoms where small percentage is treated with personal history screening7-8. Clinical findings include rigidity, tremor, drooling and impairment of liver function9.
Copper is involved in the formation of red blood cells, the absorption and utilization of iron, the metabolism of cholesterol and glucose, and the synthesis and release of life-sustaining proteins and enzymes. ... Copper also helps to neutralize "free-radicals", which can cause severe damage to cells. The variability of clinical picture of hepatic failure or bizarre neurological signs frequently slows down diagnosis in children\textsuperscript{9}. In WD chronic liver disease leads to cirrhosis; it is namedliberalbiconvexdeterioration.\textsuperscript{10} In WD hepatic, neurological, cardiac and renal compensations occurred.\textsuperscript{10} The mental adjustments coming about because of the amassing of this copper metal in the basal ganglia are some way or another less explicit. Mental highlights. Mental side effects were identified with neurological instead of hepatic symptoms.\textsuperscript{10} Copper is ingested by stomach and duodenum, reserved up by the liver, and discharged into the fundamental flow assured to ceruloplasmin\textsuperscript{11}. Wilson’s disease having not only Parkinsonism symptoms but also other manifestations likes cerebellar ataxia, epilepsy, and Young-onset dementia.\textsuperscript{13}

**CLINICAL MANIFESTATION**

The clinical manifestations of Wilson disease (figure 2) are predominantly hepatic, neurologic, and psychiatric, with many patients having a combination of symptoms [1]. Hemolysis is also a common finding in patients with acute liver failure due to Wilson disease, but sometimes may occur episodically independent of liver failure.

Patients may present with a wide variety of symptoms (especially those with neurologic symptoms) [2, 3]. Even within a given family, patients often present with different symptoms [4].
Clinical manifestations of WD vary widely but are predominantly hepatic in the first and second decades, and neurologic and psychiatric thereafter. Many patients have a combination of symptoms. WD often presents in children as chronic liver disease with abnormal liver tests. Liver pathology ranges widely, from hepatic steatosis to acute and chronic hepatitis to cirrhosis. As WD progresses, many patients develop complications of portal hypertension and liver failure. Acute liver failure (ALF) due to WD develops in about 5% of patients.

**ANIMAL MODELS OF WILSON'S DISEASE**

Four animal models of WD have been established (Figure 3): the Long-Evans Cinnamon rat, the toxic-milk mouse, the Atp7b knockout mouse, and the Labrador retriever. The existing models of WD all show good...
similarity to human hepatic WD and have been helpful in developing an improved understanding of the human disease.

Patients with WD are more likely to present with neurologic or psychiatric manifestations in their second or third decade of life. Some patients have symptoms of liver disease as well. Neurologic symptoms may be subtle or rapidly progressive, leading to severe disability over weeks to months. In patients with cirrhosis, neurologic manifestations may be mistaken for or exacerbated by hepatic encephalopathy. Some common neurologic manifestations of WD include tremor, gait abnormalities and dyscoordination, dystonia, Parkinsonism, choreiform movements, drooling, dysphonia, dysarthria or anarthria, and dysphagia. Dysautonomia may also occur, typically in patients with other neurological findings.

Behavioral and psychiatric symptoms are more common in patients with neurologic involvement than in patients with isolated hepatic involvement. However, psychiatric symptoms may precede the recognition of hepatic or neurological WD by a significant period. Behavioral and psychiatric manifestations of WD include depression, altered behavior and personality, impulsiveness and labile mood, sexual exhibitionism, and frank psychosis. When neurologic or psychiatric manifestations precede clinical liver disease, the diagnosis of WD is often delayed by 1 to 2 years.

PATHOPHYSIOLOGY

Copper is required by the body for various capacities, overwhelmingly as a cofactor for various chemicals, for example, ceruloplasmin, cytochrome C oxidase, dopamine β-hydroxylase, superoxide dismutase and tyrosinase.

The frequency of distinct neurological features of WD such as dystonia or parkinsonism varies widely in different case series. The presence of classical “wing-beating tremor” or “flapping tremor” in combination with dysarthria strongly suggests the diagnosis of WD. However, any of the other, more common forms of tremor such as rest, action, or intention tremor can occur as well. The most common form of tremor in WD is an irregular, and somewhat jerky, dystonic tremor. Dystonia is present in at least a third of all patients with a neurological presentation of WD and can be generalized, segmental, multifocal or focal. Isolated cervical dystonia is nevertheless unlikely to be due to WD. Dysarthria is frequently combined with slow tongue movements and orofacial dyskinesias including the “risussardonicus” describing involuntary grimacing with the mouth open and the upper lip contracted. Slowness of movement and other neurological features typically observed in Parkinson’s disease such as hypomimia, shuffling gait, impaired fine finger movements and foot tapping are further typical features. The presence of three distinct neurological presentations of WD has been suggested, namely 1) a dystonic syndrome, 2) an ataxic syndrome and 3) a parkinsonian syndrome.
However, the considerable majority of WD patients will present with a combination of these features. Furthermore, certain neurological features such as (dystonic) action tremor or the inability to walk heel-to-toe due to marked lower limb dystonia may be misinterpreted as cerebellar impairment with gait and limb ataxia. Pyramidal features such as pathologically brisk deep tendon reflexes can be present but paralysis is rare. The presence of sensory impairment makes the diagnosis of WD highly unlikely. Seizures also may be the presenting symptom of WD, can occur at any stage of the illness and might indeed be more common after treatment has been initiated. Vertical smooth pursuit has been reported to be abnormal in 85% of WD patients with neurological features on formal testing with electro-oculography but vision itself remains normal.

**GENETICS**

WD is a monogenic, autosomal recessively inherited condition. The causative gene ATP7B encodes a copper-transporting P-type ATPase. More than 500 ATP7B mutations have now been identified (http://www.wilsondisease.med.ualberta.ca/database.asp). Most of these are missense mutations, small deletions/insertions in the coding region, or splice junction mutations. Less common genetic mechanisms, including whole exon deletions, promoter region mutations, concurrent presence of three pathogenic alterations, and monogenic disomy, have also been observed by us and others but are comparatively rare. ATP7B mutation “hot spots” exist but vary considerably among different populations. The point mutation H1069Q is the most common ATP7B mutation in patients from Central, Eastern and Northern Europe and 50–80% of WD patients from these countries carry at least one H1069Q allele. Table 1 summarizes common ATP7B mutations in different populations.

Mutations resulting in completely absent or non-functional ATP7B protein activity are associated with early onset, typically hepatic, severe WD; these mutations are comparatively rare. Systematic attempts to establish firm genotype-phenotype correlations for other, more common ATP7B mutations have largely failed. An association between particular point mutations such as H1069Q and the late onset neurological presentation of WD was suggested but not confirmed in independent cohorts. The lack of genotype-phenotype correlations, the clinical variability and the variable penetrance suggest the presence of modifier genes that determine an individual’s level of copper tolerance or copper storage capacity. Genetic modifiers such as the presence of an E4 allele of apolipoprotein E (ApoE) or polymorphisms in the methylenetetrahydrofolate reductase gene (MTHFR) may contribute to age of WD onset but these studies await confirmation in larger, independent populations.
CASE PRESENTATION

A 42 yrs old male patient joined in Manipal hospital with a complaint of shortness of breath since 1month, continuous cough with sputum, altered behavior, icterus and history of fever since 4months on and off and generalized weakness and involuntary micturition. He had history of headaches and confusion. He had past history of diabetes for 4yrs and history of schizophrenia for 3yrs. He had no family history. The patient's appetite was decreased, bowel irregular, micturition involuntary and disturbed sleep. The physical examination reveals that pulse 116/min, BP 110/70mmhg, pallor, icterus, and lymphadenopathy found. Systemic examination reveals all systems are normal. Figure 2 shows Endoscopic impression was portal HTN-low grade changes only, distal oesophageal ulcers-likely sources of recent GI bleed on 13/9/19. Figure 1 shows MRI brain impression was bilateral symmetrical T1 hyper intensity in Globus Pallidus on 13/8/19. 2DECHO impression was tachycardia, normal cardiac chambers, No RWMA of LV, normal LV systolic function, trivial MR/TR NO PAH, No clot/veg effusion USG impression was found to be choric liver disease mild splenomegaly mild gall bladder wall oedema mild ascites. Liver function test found to be serum creatinine 0.7mg/dl, total bilirubin 2.98 mg/dl, direct bilirubin 1.56mg/dl, indirect bilirubin 1.42mg/dl, SGOT 43 IU/L, SGPT 18IU/L, ALP 82IU/L, total protein 6.2g/dl, serum albumin 1.9g/dl, serum globulin 4.3g/dl and A/G ratio 0.44 on 15/10/19. Serum sodium 108.5mmol/L, serum potassium 4.4mmol/L, serum chloride 108.5mmol/L on 11/10/19. Thyroid values found to be T3 0.98ng/ml, T4 6.69micg/dl, and TSH 4.260miCIU/ml on 9/9/19. Prothrombin time found to be 21.9sec, WBC count 5600/cumm, RBC count 3.30million/cumm, haemoglobin 11.8g/dl, PCV 35.2%, MCV 106.6fl, MCH 35.8pg, MCHC 33.6g/dl, platelet count 62000/cumm, RDW 23.9%, neutrophils 70, lymphocytes 16, monocytes 7, eosinophils 7 on 11/10/19. The diagnosis was Wilson's disease with HP syndrome. The MRI and USG investigations are shown in Fig.1

Discussion:

Wilson’s disease is defined as a rare autosomal recedingsyndrome due to the excess copper accumulation. Maximumcasesarestatedindevelopedcountries.TherearetheredifferenttypesofWilsondiseasebased on genetic variability. The juvenile type appears before 16-years of age and is mostly a liver disease before 5 years\cite{18}. The salvia type appears after 16 years of age and is mostly a neurological disease. The serum ceruloplasmin remains normal to these two types of the disease (Swaiman et al. 1982). The third type, classified as atypical Wilson disease is characterized by low serum ceruloplasmin level and clinical picture similar to those of juvenile type (Misra et al 1988, Cox et al 1972). The patient had atypical form of the disease with low ceruloplasmin level. Those excellent presentation needs been described by Agdistis toward onset the middle of 5 Furthermore 40 years, perceivable Kayser-Fleischer rings, and diminished serum ceruloplasmin. Those patients for liver infection don't help those two of the parameters in three criteria, it prompts those symptomatic unreliability\cite{19}. Recently, symptomatic developments need
permitted for an all the more deliberate methodology to finding. American affiliation for those examines of liver ailments rules gives an deliberate methodology for supporting for the finding about WD. On our patient, indications reliable for WD included cirque., schizophrenia, confusion, cough with sputum, fever, and headache. He was a known case of DM, CLD with portal hypertension. Postponement in taking decision and the start of chelation therapy unfavorably disturb the predictions for improved outcomes. 

**Figure 1. Details of MRI and USG investigations of the patient**

**Conclusion:**

The standard therapy for Wilson disease is copper chelating agents (D-penicillamine or Trientine) or zinc, Dimercaprol can reduce hepatic neurologic and psychiatric findings. Orthotopic liver transplantation is used aimed at individuals who failed to react to medicinal treatment or current by fulminant acute liver failure. The patient was a chronic schizophrenic for 15 years and using Tab. Paliperidone 3mg OD, Tab. THP (trihexyphenidyl) 2mg OD, Tab. Lorazepam 1mg SOS; after admitting hospital-physician advised to stop Palliperidone and THP and using Inj. Lora+Serenace 1amp. As copper toxicity is due to ATB7B deficiency in Wilson disease produces liver injury So there is a need for liver transplantation, done in this patient and given supportive therapy like antibiotics such as Meropenam500 mg.

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