Abstract:
Wilson’s disease is a neurodegenerative disease of copper metabolism. Normal dietary consumption and absorption of copper exceed the metabolic need, and homeostasis of this element is maintained exclusively by the biliary excretion of copper. In Wilson’s disease, the defective biliary excretion of copper leads to its accumulation, particularly in liver and brain. The deposition of copper in tissues is the cause of virtually all the manifestations of the disease - cirrhosis, hemolytic anemia, renal tubular changes, Kayser-Fleischer rings and the cerebral damage. Here we present a case report of a young girl who presented to us with sudden onset of neuropsychiatric symptoms such as involuntary twisting movements, abnormal postures and cognitive impairment but without any form of hepatic involvement - a fairly uncommon presentation of a rather familiar disease. Achieving a diagnosis of Wilson’s disease is dependent on maintaining a high index of suspicion. This is very important because early initiation of treatment will cause significant reduction in morbidity and mortality. Untreated Wilson’s disease is universally fatal, with most patients dying from liver disease and a minority from complications of progressive neurologic disease.


INTRODUCTION
Wilson’s disease or hepatolenticular degeneration is a neurodegenerative disease of copper metabolism. It is an autosomal recessive disorder that results in clinical manifestations caused by copper toxicity mainly involving the liver and brain.

In 1912, Samuel Kinnier Wilson first described it as a familial disorder associated with neurological symptoms and cirrhosis. Clinical presentation can vary widely, but the key features of Wilson’s disease are liver disease and cirrhosis, neuropsychiatric disturbances, Kayser–Fleischer rings in Descemet’s membrane of the cornea, and acute episodes of hemolysis often in association with acute liver failure. Wilson’s disease is not just a disease of children and young adults, but may present at any age.

CASE REPORT:
A 16 yr old female (fig.1), was brought to the OPD by her mother with a one month history of abnormal posturing of her neck and her left upper and lower limbs associated with progressive cognitive decline and speech disturbances.

As per the history given by her mother, our patient was quite normal one month back – there were no disturbances in movement, speech or mood. The abnormal twisting movements in her neck and limbs were painful and present throughout the day. She had difficulty in speaking and swallowing. Her mother complained of “childish” behavior and frequent mood swings noticed since one month. There was no history of fever. No jaundice, hematemesis, melena or any other bleeding manifestations. No bowel or bladder disturbances.
Wilson’s disease is due to a defect in the copper-transporting P-type ATPase secondary to mutations in the ATP7B gene located on chromosome 13q14.3. The mutation gives rise to two fundamental disturbances of copper metabolism:

(i) reduced rate of incorporation of copper into ceruloplasmin and (ii) a reduction in biliary excretion of copper[1].

Before puberty the common onset is liver damage: this may range from a self limiting hepatitis through chronic active hepatitis to cirrhosis. A neurological presentation is uncommon in this age group. After puberty neurological signs and symptoms involving the motor, but not the sensory nervous system, predominate. They are quite frequently associated with a change in personality and a failing performance at school.[2]

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 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]

This is in contrary to our patient who had presented with sudden onset, rapidly progressive neuropsychiatric symptoms and severe bulbar muscle dystonia causing spastic dysarthria and dysphagia but without any hepatic involvement. This is quite unusual because of the younger age of onset and rapidity of progression of symptoms, one would expect at least some degree of hepatic disease. But her liver function tests and ultrasound of liver were absolutely normal.

A previous study by Walshe and Yealland describes four distinct diagnostic categories based on patients’ major neurological findings:

1) Parkinsonian group (45%) distinguished by the paucity of expression and movement;
2) Pseudosclerotic group (24%) had tremor resembling multiple sclerosis;
3) Dystonic (15%) group characterized by hypertonicity associated with abnormal limb movements;
4) Choreic group (11%) characterised by choreoathetoid movements; 4% fitted into no specific category.[5] There may be significant overlap between these groups.

Our patient who presented with dystonia of bulbar muscles, neck and limbs falls into the 3rd group that constitutes only 15%.

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 only 10% of asymptomatic siblings[6]. Other ophthalmologic changes are rare and include sunflower cataracts, which are caused by deposits of copper in the center of the lens. They can also be found by slitlamp examination[7]. Our patient had this rare finding of bilateral Sunflower Cataracts and didn’t have any significant visual impairment.

Leipzig Diagnostic Criteria was proposed in Leipzig Germany 2001 at the 8th international meeting which recommends the presence of SF rings, low serum ceruloplasmin and high 24 hour urinary copper excretion in patients with neurological symptoms for diagnosis of Wilson’s disease.[8]

DISCUSSION

Wilson’s disease is due to a defect in the copper-transporting P-type ATPase secondary to mutations in the ATP7B gene located on chromosome 13q14.3. The mutation gives rise to two fundamental disturbances of copper metabolism:

Her developmental milestones were normal. She had not attained menarche. She was educated upto 8th std and had dropped out of school at 14yrs age due to difficulty in studying. There was rapid decline in scholastic performance between 12 and 14 yrs age.

She had 2 sisters and both were normal. There was no family history of similar complaints or any neurological illness. No recent drug intake.

Her routine lab investigations:

- Complete blood count: Hb - 10.8g/dl, TC - 8,600/cu.mm., Platelets - 1.8 l/cu.mm
- Blood sugar – 86mg/dl
- Renal function tests:
  - urea - 28mg/dl, creatinine - 0.8mg/dl
- Liver Function tests:
  - S.Bilirubin - 1.0 mg/dl
  - SGOT - 28 U/L, SGPT - 22 U/L
  - S.Alkaline phosphatase – 111 U/L
  - S.Albumin - 3.5 g/dl
  - S.Globulin - 2.5 g/dl
- Prothrombin time - 17.1 secs, INR - 1.45
- USG Abdomen showed normal study.

CT Brain – Normal study

On examination, she was conscious, oriented, afebrile, no pallor or icterus. Bilateral cataracts and Kayser Fleischer rings (fig.2) were present that were visible to the naked eye.

Neurological examination revealed MMSE 20/30, bulbar muscle dystonia that caused dysphagia & spastic dysarthria, emotional instability, dystonic posturing of her neck and left upper limb (as shown in fig.1) with increased tone. Her vitals and other systems examination were found to be clinically normal.

Fig.2

Serum Ceruloplasmin –2.85 mg/dl ( Normal = 18 – 35 mg/dl )
24hrs urinary copper – 520 μg/day ( Normal = 20 – 50 μg/day)

The presence of neuropsychiatric manifestations, KF ring, elevated urinary copper and low Serum Ceruloplasmin levels were sufficient to diagnose Wilson’s disease in our patient. She was started on oral Zinc acetate 50mg tds, Trihexyphenidyl 4mg tds and Baclofen 10mg bd.

The peculiarities in our case were that the patient was a young girl with pure neuropsychiatric manifestations without any form of hepatic involvement and a normal CT imaging of the Brain despite the severity of her neurological symptoms. She had presented with a rare finding of bilateral Sunflower cataracts. I would also like to emphasize the importance of clinical examination that detected the KF rings which helped clinch the diagnosis of Wilson’s disease as a cause of secondary dystonia in this adolescent female who presented only with neuropsychiatric manifestations and without any clinical or biochemical hepatic abnormalities or significant family history.
Zinc is used as first line therapy in neurological patients. Zinc interferes with the uptake of copper from the gastrointestinal tract. Zinc induces enterocyte metallothionein, a cysteine-rich protein that is an endogenous chelator preferentially binds copper present in the enterocyte and inhibits its entry into the portal circulation[9]. Ammonium tetrathiomolybdate (TM) is a very strong decoppering agent. It complexes with copper; in the intestinal tract it prevents absorption, and in the circulation renders copper unavailable for cellular uptake[10]. TM remains an experimental therapy, and it is not commercially available. As yet, clinical experience with this drug is limited. Antioxidants, mainly vitamin E, may have a role as adjunctive treatment[11].

COMMENT

Wilson's disease is one of the very few chronic, progressive degenerative diseases of the nervous system for which there is a specific and effective treatment. It is a serious mistake to miss the diagnosis or suffer such a delay in making it that irreversible damage occurs to the central nervous system or liver. All young patients, below the age of 40yrs, presenting with neurological or psychiatric features as initial manifestations should be thoroughly screened for Wilson's disease in order to enable early treatment for the patient and screening of the relatives.

REFERENCES

1. Harrison's Principles of Internal Medicine, 18th Ed.