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RESEARCH ARTICLE

ATYPICAL PRESENTATION OF WILSON'S DISEASE WITH STATUS EPILEPTICUS

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ABSTRACT

Wilson's disease is a rare autosomal recessive disorder, leads to the impairment in copper transport characterized by accumulation of anomalous amount of copper in the body tissues especially in the liver. The classical clinical presentation of the Wilson's disease include presence of Keyser-Fischer ring, low serum ceruloplasmin levels and increased 24 hrs urinary copper levels. Here we present a case of 15 year old young girl who does not have classical clinical features of Wilson's disease, rather she presented with psychotic onset, hepatic failure, near normal serum ceruloplasmin levels, status epilepticus and absent Keyser–Fischer rings. The Diagnosis confirmed with help of urinary copper values and brain CT scan. Wilson's disease can be veiled for a long time with the psychiatric and neurological symptoms and rarely it may be complicated with frequent seizure attacks and it may be harmful for the patient. In this kind of unequivocal cases, mutation analysis is an imperative diagnostic measure.

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INTRODUCTION

Wilson disease (hepatolenticular degeneration) genetically inherited disorder thatleads to impairment of cellular copper transport.It is having a prevalence rate of approximately 1 in 30,000 live births in the world populations. Impaired biliary copper excretion causes the accumulation of copper in various organs in the body, dreadfully in the liver, brain etc. The liver is graduallyinjured and ultimatelyturns into cirrhotic. A minutepercentage of patients having acute liver failure. Patients may also at risk for neurological problems, which may be severe in most of the cases. Copper is get absorbed in the stomach and duodenum, combines principallywith circulating albumin, and is pick up by various tissues. If the daily requirement for copper exceeds, it is predominantly excreted into the bile. The copper transport within hepatocytes is synchronized by ATP7B gene. In the ER-Golgi network, ATP7B arbitrates the transport of copper by binding with ceruloplasmin; a ferroxidase enzyme that present in human body and is encoded by CP gene and it isone of the key copper-carrying protein inthe blood. Copper in ceruloplasmin is not transferableunder normalphysiologic conditions. Wilson disease exemplifies an autosomal recessive pattern due the mutation in ATP7B, a gene encoding a hepatic copper transport protein (ATP7B) on chromosome 13. Mutation in ATP7B impair both the incorporation of copper into apoceruloplasmin and the excretion of copper into bile, hindering vital pathway of copper elimination and upshot the clinical manifestations of Wilson disease. In patients with Wilson'sdisease, excess copper in the body primarily bound to metallothionein; a cystine rich low molecular weight and distributed evenly throughout the cytoplasm. With progressive copper accumulation, the capacity of metallothionein is exceeded, dense lysosomal copper deposits develop, and hepatocyte injury develops. The occurrence of Wilson's disease in menand women are all most the same, however women are more prone fordeveloping acute liver failure than that of the men and men were more likely than women to have neuropsychiatric problems. The commonly themean age atdiagnosis of Wilson disease is between 12 to 23 years. The clinical features of Wilson disease are mainly hepatic, neurologic, and psychiatric, with many patients having a combination of symptoms. The liver is the primary site of copper accumulation in patients with Wilson disease; involvement of liver shows the features of liver cirrhosis along with the abdominal pain, Jaundice, Splenomegaly, Upper gastrointestinal bleeding, Mental status changes due to hepatic encephalopathy, coagulopathy etc.

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The most predominant ocular manifestation of the Wilsons disease is a bilateral green brown granular deposit of copper in Descement's memebrane around the corneal limbus - Kayser-Fleischer rings which is seen nearly 98% of patients. Majority of patients with neurological Wilson'sdisease having dysarthria, ataxia, dystonia, tremor Parkinsonism, drooling etc. Certain patients are complicated with athetosis, cognitiveimpairment, seizures, hyperreflexia etc.

Behavioral and psychiatric symptoms are more prevalent in patients with neurologic disease than in patients with hepatic disease. The most common behavioral and psychiatric symptoms include depression, personalitychanges, impulsiveness, inappropriate behavior, psychosis etc.In some cases, the initial manifestations of the disease can be psychiatric which accounts for only 10% of the cases. Isolated behavioral problems, an irrational syndrome, a schizophrenic syndrome, or a manic-depressive syndrome can reveal the disease. However, behavioral and psychiatric symptoms due to Wilson disease are often misdiagnosed in the earlier phases of the disease. Testing starts with serologic testing such as liver biochemical tests, a complete blood count, and serum ceruloplasmin level, an ocular slit-lamp examination, and 24-hour urinary copper excretion etc. Typically patient with Wilson disease having changes in the serological investigations which may point out that there is a problem present in the functioning of the kidney and the liver –aminoaciduria. The normal range for ceruloplasmin in the blood is between 20 and 50 milligrams per deciliter. Ifthe levels are less thanthe normalrange, it may indicate the presence of Wilson's disease. Most often the level of serum copper is also seems to be low. The urinary copper excretion rate is greater than 100 µg/dl (reference range, <40µ g/dl) in most patients with symptomatic Wilson disease. The CT scan divulges hypo dense regions in the basal ganglia and cerebrocortical atrophy. Mutation analysis is animportant diagnostic approach for populations demonstrating anarrow spectrum of ATP7B mutations. The combination of the characteristic signs and symptoms along with keyser-Fischer ring andlow ceruloplasmin levels are considered as the golden tool for the diagnosis of the Wilson's disease.

Lifelong treatment is intended primarily at treating copper overload is required in patients with Wilson disease, and treatment is planned in two phases: removing or detoxifying the tissue copper that has accumulated and preventing reaccumulation.Copper removal is accomplished by the administration of effective chelators. The primary chelator that has been used is D-penicillamine. Other medications such as sodium dimercaptosuccinate, dimercaptosuccinic acid, zinc, and tetrathiomolybdate are also used to chelate the excess copper. With clinical progression, acute liver failure, or worsening hepatic function, the patient must be assessed and the check possibility for performing liver transplantation. Patients are also advised to avoid eating foods with a high copper content.

CASE REPORT

A 15-year-old girl without momentous medical history formerly known as a healthy subject and she had no history of herbal medications and any kinds of supplements. Her mother had an history of jaundice andshe wasexpired four year back. In the summer vacation thiswas girl suffering from jaundice and did not have any history of recent family history of jaundice. One month before the admission she ran out from the school with a harsh cry and thereafter having altered behavior pattern showing aggression towards the family members, reduction in socialization and shows wide delusions and suicidal ideations. She was treated at a psychiatric centre and diagnosed as schizophrenia. A 2 months long treatment with anti-psychotics such as Quetiapineand Haloperidol along with Olanzapine.Unfortunately she did not show any improvements even though with the treatment, but one week before the recent hospitalization she having two episode of tonic-clonic seizure and yellowing of the sclera, high coloured urine and bilious vomiting. On admission, patient was febrile, eupnoic and normotensive with pallor and yellow discolouraion of sclera. Mental status examination revealed that the patient was conscious but disoriented and irritable, showing negativism, low socialization and impulsive behaviour. Neurological examination revealed that no other abnormalities except rigidity of upper limbs.On abdominal examination evident that hepatosplenomegaly and the liver span is 11 cms, with moderate ascitis.She also having terrynails, flapping tremor along with constructional apraxia. Her diagnostic investigations reveled that Hb-9 g %,Bilirubin-4.2 mg/dl, ALP-193 IU/L, AST-64 IU/L, ALT- 37 IU/L, Blood urea 28 mg/dl ,PT-control13.6 sec test 16.6 sec, INR 1.62.Lumbar puncture was done and the CSF analysis showed normal range. EEG was normal.

While keeping the patients clinical profile in mind the medical team decided to investigate the possibility of autoimmune hepatitis and Wilson's disease.Pateint's IgG value is 1134 mg/dl (716-1711 mg/dL) and antinuclear antibody (ANA) profile is negative. On the initial slit lamp examination the Keyser-Fleischer ring was absent along with serum ceruloplasmin – 18 mg/dl (20-35 mg/dl), serum copper - 14 mmol/l (11.90-20.41 mmol/l). 24 hrs urinary copper test was very high in this patient and the value is 487 µg/dl (<100µg/dl). The resultswas rechecked to confirm the diagnosis of Wilson's disease. The 24 hrs urine copper value become 642µg/dl, even though the other parameters suggests the possibility of Wilson's disease but the Keyser-Fleischer ring was absent. So the team also prescribed a CT scan of brain suggested that hypodense regions in the basal ganglia, Ventricular enlargement and posterior fossa atrophy. These investigation findings and patient's clinical profile suggest that this is a case of Wilson's disese. Patient was started on oral Pencillamine, mannitol, multivitamin, Vitamin K along with anticonvulsants. But even with 2 weeks of treatment the girl had gradual deterioration in the neurological status as well as hepatic functioning but the 24 hrs urine copper values were lesser than the initial stage. During the course of treatment suddenly she developed three repeated episodes of tonic clonic seizures.The medical team discussed the condition again and finally decided to take the patient for livertraspalation. Unfortunately, patient again having repeated seizureattacks and her vital parameters get diminished even with all resuscitative measures and she passed away.

DISCUSSION

In the present case, the young girl presented with many specific features that make a distinction from other patients with Wilson's disease. The main oddity consists of fulminant hepatic failure which is uncommon and is a rare feature of Wilson's disease. The another interesting thing in this patient's history is the insidious onset of the psychiatricmanifestations

and she underwent nearly 2 months of treatment with antipsychotics. Unfortunately this feature may hide the possibility for the prompt diagnosis as in similar cases described elsewhere. At the initial course of the disease the patient had an episode of jaundicebut it was subsided during the course of treatment and it occurred in the later stages of the disease. Along with mother's jaundice history the team forced to check the possibility of autoimmune hepatitis but the immunological profile was negative. But an interesting part in this case was the K-F ring were absent on the slit lamp examination, it may be seen in 10-50 % of patient with the Wilson's disease. Patient's serum ceruloplasmin levels were 18 mg/dl, which may even in the lower range, but in typical presentations it is usually less than 10 mg/dl. The ceruloplasmin level may be elevated even with the acute inflammatory liver diseases, this possibility excluded in this case by testing the 24 hrs urinary copper excretion, that was gradually increased by time to time. But the urine copper value may elevate in chronic cholestasis and copper toxicity. Due to the instability of coagulation profile and general condition of the patient hepatic copper concentration determination was not done and finally decided to rule out the causes of seizure and CT brain was advised and this shows typical basal ganglia thickening. This is all collectively pointed out to the chance for Wilson's disease. After the pencillamine therapy started the patient had reduction in the urine copper value. But she had uncontrollable seizure. Epileptic seizures are reported to be rare in Wilson's disease, occurring in about 6–7% of cases. The epileptogenic activity because of the copper deposition in various parts of cerebral cortex or may be due to the probable outcome of treatment with penicillamine. The death of the patient may be due to seizure induced cardio-respiratory arrest.

Conclusion

Atypical presentations of the Wilson's disease can remain undiagnosed for a long period and it may be misinterpreted as other systemic diseasesbased on the clinical manifestations. In these type of cases can be better diagnosed by genetic/mutation analysis. Hypocupremic states should be kept in mind as a risk factor for resistant seizures. Early diagnosis and effective treatment definitely improve the outlook. The prognosis of the Wilson's disease is better before the occurrence of irreversible complications.

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