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ATYPICAL PRESENTATION OF WILSON'S DISEASE

General Medicine

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ABSTRACT

A 17-year-old boy, who was eventually diagnosed with Wilson's disease (WD), was initially seen with gradually progressive weakness for at least 4 months prior to developing more typical symptoms of the disease. The clinical presentations of WD are protean and varied. The phenotypic variability of WD often leads to delay in diagnosis, unless there is a high index of suspicion. In a large series of 307 patients of WD, evaluated at NIMHANS, Bangalore, misdiagnosis at initial evaluation was recorded in 62.5% cases, leading to a mean delay of two years in arriving at correct diagnosis and initiating treatment. Musculoskeletal involvement in WD is uncommon; in a large series only 22 of 282 (0.07%) patients with WD manifested muscular symptoms. Early diagnosis and treatment may prevent serious long-term disability and life threatening complications. Combination of an elevated creatinine kinase (ck) with transaminase elevation guide primarily to assumed diagnosis of neuromuscular disease. In rare cases an elevated ck with musculoskeletal symptoms can be the initial manifestation of Wilson disease. An early diagnosis of Wilson disease is important to avoid a toxic concentration of copper in the tissue.

KEYWORDS

Wilson's disease, muscular weakness

INTRODUCTION

Wilson's disease (WD) is a rare autosomal inherited disorder of copper metabolism that is characterized by excessive deposition of copper in the liver, brain, and other tissues. Clinical symptoms appear most commonly during the second decade although rarely may be delayed until the fifth. Early recognition of this disease is difficult because all too often it is simply not considered in the differential diagnosis. Frequently patients with Wilson's disease are obscured by being followed in large neurology outpatient clinics with symptoms of Parkinsonism, peripheral neuropathy, muscle disease or as cases of juvenile cirrhosis of unknown etiology.1 In this case report, we describe a young patient with Wilson's disease who presented with difficulty in walking and spasmodic lower extremity muscle cramps.

CASE REPORT

A 17-year-old boy from a rural background and lower socioeconomic class (education up to the 4th standard) presented to the medicine outpatient department with progressive difficulty in walking and climbing stairs for past few months and spasmodic lower extremity muscle cramps. These symptoms have been present for about 4 months and worsened gradually. He had no remarkable medical or family history of liver disease, psychiatric illness, or movement disorders. He was second born to a third-degree consanguineous couple with unremarkable family history. He was not a habitual alcohol or drug abuser.

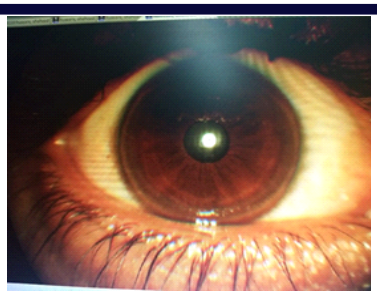
On examination, he had normal anthropometry and vital parameters. Abdominal examination revealed palpable liver 3cm below the costal margin in mid-clavicular line with firm consistency. He had a mild splenomegaly without any venous prominence and clinical evidence of free fluid in the abdomen. Although he was oriented but some cognitive deficits in the form of slow responses was noted. There was also history of decline in school performance and subtle behavioural and personality changes. Cranial nerve examination results were normal. The neurological examination revealed hypotonia and weakness in all four limbs, the power being about 3/5 in bilateral lower limbs and 4/5 in upper limbs. The weakness was more proximal than distal and was associated with significant flaccidity but without fasciculations, sensory abnormalities or diurnal variation. Muscle bulk was normal. The sensory examination results for soft touch, pain, temperature, vibration, and proprioception were normal. Deep tendon reflexes were symmetrically present in the biceps, triceps, knee, and ankle. Gait was wide based; short strides with tendency to fall.

Initial testing revealed creatinine kinase of 353 IU/L (normal 23–195 IU/L), hemoglobin of 8.9 g/dL (11.5–15.5 g/dL) and myoglobinuria. Serum electrolytes including serum potassium were within normal limits. Other laboratory investigations revealed total bilirubin of 2.7 mg/dl, aspartate aminotransferase of 108 IU/L and alanine aminotransferase of 47 IU/L ,serum albumin of 3.3 and alkaline phosphatase of 50 (normal range from 45 to 110 mU per ml). Antinuclear antibodies, HBsAg and antihepatitis A virus were negative.

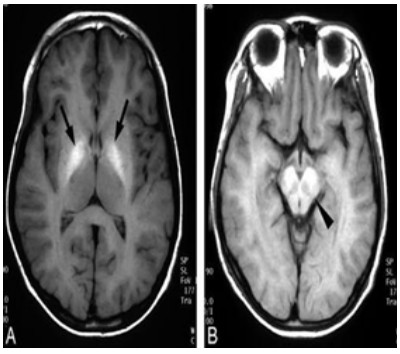
Abdominal ultrasound was normal except for mild hepatomegaly and splenomegaly Evaluation for muscle disease by means of magnetic resonance imaging (MRI) and Electromyography (EMG) was normal. Muscle biopsy was refused by the patient's family. In addition, repeated neurological examinations showed no evidence of hereditary muscular dystrophies.

In view of abnormal liver function tests (although there were no symptoms suggestive of liver dysfunction) patient was also evaluated for common causes of chronic liver disease. As he was only seventeen yrs of age and also there was some history of behavior problem, the diagnostic possibility of Wilson' disease was considered. Further investigations revealed that serum ceruloplasmin was markedly reduced at 0.164 g/L (reference values: 0.204–0.407 g/L);copper concentrations were significantly decreased at 50 µg/dl (reference range: 70–153 µg/dl) and 24-h urinary copper was high at 240 µg/24 h (volume: 1690 cc) (reference value up to 80 µg/24 h; WD >100 µg/24 h). Slit-lamp examination showed the Kayser–Fleischer (KF) ring.

Ophthalmological slit-lamp examination demonstrated the initial development of Kayser–Fleischer (KF) rings in the clear anterior segment of the cornea.



MR Brain study shows symmetrical bilateral basal ganglia and dorsal pons T2/Flair hyperintensities suggestive of Wilson's disease.



Hence, a diagnosis of WD with muscular involvement was considered. He has been initiated on oral penicillamine at 20 mg/kg/day, oral zinc 25 mg thrice daily. Trientine could not be given due to its unavailability in the country

DISCUSSION

The clinical presentations of WD are protean and varied. Walshe2 has aptly stated that no two patients of WD have similar clinical characteristics even among the common sib-ship ,stressing its diverse manifestations. The phenotypic variability of WD often leads to delay in diagnosis, unless there is a high index of suspicion. In a large series of 307 patients of WD, evaluated at NIMHANS, Bangalore, misdiagnosis at initial evaluation was recorded in 62.5% cases, leading to a mean delay of two years in arriving at correct diagnosis and initiating treatment. The common presenting symptoms in this series were: tremors 97, dysarthria 48, jaundice 38, abnormal gait 27 and abdominal distension 24, musculoskeletal complaints 16, seizures 15, behavioural problems 14, dystonia 11, clumsiness 8, drooling 8, decreased activity/generalised weakness 7, decreased scholastic performance 6, changed sensorium 4, bleeding symptoms 4, dysphagia 3, chorea and poor vision, one each.[3]

Musculoskeletal involvement in WD is uncommon with bone demineralization, arthropathy, or hypokalemic muscle weakness being more common. In addition, skeletal and cutaneous abnormalities in Wilson's disease have also been described. The skeletal disorders that may occur include osteoporosis, osteomalacia, osteoarthritis, osteochrondritis, sclerosis, and intra-articular calcifications. Pigmentation of the nails and skin, particularly on the shins, has been observed. However, it is not clear whether and to what extent these phenomena reflect copper toxicity4,5. In a large series, Taly et al. had reported only 22 of 282 (0.07%) patients with WD manifesting with muscular involvement.[6]

Though hepatic involvement occurs early in the course of WD, it may go unrecognized and may not be the first symptom for seeking clinical attention as was the case with our patient.

About the pathogenesis of Wilson's disease, the incorporation of copper to ceruloplasmin and excretion of copper into bile are impaired. Excess copper generates free radicals resulting in oxidation of lipids and proteins. It then accumulates in liver and damages the hepatocytes. Once the liver copper level increases, it starts getting deposited in other organs also. The deliverance of free copper into the blood is known to cause haemolysis and renal tubulopathy. The copper deposits in peripheral muscle tissue may be the possible explanation for the muscular symptoms in our patient.

The copper deposits in peripheral muscle tissue have rarely been reported. However, cardiomyopathy with definite morphological abnormalities has been described in Wilson's disease with the presence of interstitial and replacement myocardial fibrosis, intramyocardial small vessel disease, focal myocarditis, and cardiac hypertrophy as the major pathological findings. These alterations are in some cases of limited severity but are similar to those observed in hemochromatosis and seem to be proportional to the cardiac concentration of copper.7,8 . A case of a young patient with Wilson's disease who developed recurrent episodes of acute rhabdomyolysis has been described 9 . The present recurrent hypokalemic paralysis due to renal tubular acidosis is a rare initial presentation of WD have been described10 Experimentally copper accumulation in skeletal muscles is known to cause signs of muscle degeneration as early as 3 days[11]

Thus, probable mechanism of myopathy in WD could be due to intracellular copper accumulation in the skeletal muscles leading to oxidative stress, free radical formation, secondary mitochondrial dysfunction and cell death. In our patient , 3 months after the iniation of treatment, the muscular weakness was substantially resolved, suggesting the direct effect of copper. We describe this case to highlight that though rare, muscular involvement can be a presenting manifestation of WD usually associated with evidence of hepatic or CNS involvement. Absence of calf muscle hypertrophy, normal creatine phosphokinase, normal nerve conduction studies and KF ring on slit-lamp examination might be additional clues to clinch the diagnosis.There is a need for specialists in these and related fields to be aware of hints from within and, more importantly, outside their area of expertise that should alert them to consider the diagnosis. Delayed diagnosis and treatment are potentially damaging for the patient. The importance of recognising and promptly investigating Wilson disease at the initial presentation should be understood by all those who assess patients with hepatic or neurologic disorders and/or train others in their specialty[13]

CONCLUSION

Combination of an elevated creatinine kinase (ck) with transaminase elevation guide primarily to assumed diagnosis of neuromuscular disease. In patients with unexplained musculoskeletal symptoms and hepatic abnormalities, a diagnosis of. WD should be considered and appropriate evaluation initiated. An early diagnosis of Wilson's disease is important to avoid a toxic concentration of copper in the tissue. In rare cases, elevated ck and muscle weakness can be initial symptoms of Wilson disease. An extended hepatologic diagnostic should be executed particularly when associated with accompanying elevated GGT. The existence of an associated neuromuscular disease has to be discussed when the elevated ck or the muscular symptoms persist despite an appropriate therapy.

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