Wilson Disease with Visceral Leishmaniasis: An Extremely Uncommon Presentation


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Abstract. Visceral leishmaniasis (VL), which is caused by the protozoa Leishmania donovani and transmitted by the bite of the female sand fly Phlebotomus argentipes, is common in Bihar, India. Wilson disease is an autosomal recessive disorder of copper metabolism in which copper is deposited in the brain and liver. We report a case of an extremely uncommon combination of these diseases in a patient. Treatment options for such a combination of diseases are limited and difficult.

INTRODUCTION

Visceral leishmaniasis (VL), a protozoal disease, is caused by Leishmania donovani and transmitted by bite of female sand fly (vector) Phlebotomus argentipes. It is estimated that 600,000 new cases of VL occur globally per year.2 Approximately 90% of these cases are reported in India, Brazil, Bangladesh, Sudan, and Nepal. In India, approximately 80% of VL cases are reported in Bihar State; the remainder are reported in Eastern Uttar Pradesh, Assam, and West Bengal.3 The disease affects mainly poor people.3 It is characterized by prolonged fever, hepatosplenomegaly, pancytopenia, and emaciation. The disease is fatal if left untreated.4

Wilson disease is an autosomal recessive disorder of copper metabolism. Defective copper metabolism leads to systemic accumulation of copper, which can cause progressive liver damage, neurological deficits, psychiatric illness, Kayser’s Fleischer (KF) rings, arthropathy, cardiomyopathy, and renal tubular disorders.5

The worldwide prevalence of Wilson disease has been reported to be approximately 1 in 50,000 with a carrier rate of 1 in 90.6 The abnormal gene resides on chromosome 13 in the region of 13q14. The gene, known as ATP7B, codes for a membrane-bound copper-binding ATPase.6 Little research has been conducted on the incidence and spectrum of mutations causing Wilson disease in persons in India. The Indian population has a high degree of mixing and out-breeding, being elderly and multi-ethnic. Thus, the possibility exists for high heterogeneity in the mutation profile. Wilson disease, which is a rare disease, can have a few prevalent mutations in the population due to the founder effect.7

CASE REPORT

In April 2006, a 13-year-old boy brought to the outpatient of Rajendra Memorial Research Institute of Medical Sciences. He had an irregular fever for two months, and severe anorexia, anemia, and weakness. He reported difficulty in walking and writing. He also had wing beat tremor along with mask-like facies. There was no family history of a similar type of disease in previous generations as his siblings. He was born out of a non-consanguineous marriage.

On examination, the patient appeared pale, febrile (38°C), and had hepatosplenomegaly. Both the liver and spleen were enlarged approximately 4 cm below the respective costal margins. He had mild ascites. He had a pulse rate of 110/minute and a respiratory rate of 22/minute. Neurologic examination showed grossly increased tone (rigidity) with a power grade of 3–4/5 in all groups of muscles in the upper and lower limbs. He also had choreo-athetotic dystonic movements in the upper and lower limbs. Coordination was impaired probably because of dystonic movements. He had dystaria and dysphagia. Plantars were bilaterally flexor and the reflexes were normal (superficial, deep, and visceral). Results of a sensory examination were normal. The characteristic wing beat tremor was present when his arms were extended. His gait was spastic. He appeared to have psychosis (attacks of inappropriate laughter and crying) with drooling from the mouth. Neck rigidity and Kernig’s sign were negative.

Laboratory examination showed a hemoglobin level of 7.0 g/dL (normal range = 12.0–15.0 g/dL) with pancytopenia. Liver function tests showed a bilirubin level of 2 mg/dL (normal range = 0.1–1 mg/dL) and an alanine aminotransferase level of 40 units/L (normal range = 9–43 units/L). His alkaline phosphatase level was within the normal range (80–306 units/L) and his prothrombin time was 5 seconds within the normal range (12–16 seconds). He had a low serum albumin level and a reversed albumin: globulin ratio. Kidney function tests showed normal levels of blood urea nitrogen and serum creatinine (normal ranges = 5–25 mg/dL and 0.7–1.1 mg/dL). There was no albumin in a morning urine sample. Serum electrolytes (sodium, potassium, and chloride) levels were within normal limits.

He was subjected to splenic aspiration, which showed numerous Leishmania donovani (LD) bodies (3+ as per the World Health Organization criteria). Results of a chest radiograph were normal and enzyme-linked immunosorbent assay results for human immunodeficiency virus, hepatitis B surface antigen, and hepatitis C virus were negative. Ultrasound of the abdomen showed hepatosplenomegaly with altered homogeneous echo texture and prominent portal varices suggestive of portal hypertension, with few enlarged mesenteric nodes. He had a serum copper level of 82.6 μg/dL (normal range = 70–140 μg/dL) and a serum ceruloplasmin level of 20 mg/dL (normal range = 20–60 mg/dL by the nephelometry method) and a urinary copper excretion rate of more than 100 μg/24 hours. His erythrocyte sedimentation rate and level of C-reactive protein were increased. A computerized tomographic scan of the brain showed basal ganglia calcification bilaterally. The patient was sent to an ophthalmologist who confirmed KF rings in both eyes on slit lamp examination.

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Based on the above clinical and laboratory findings, a diagnosis of VL and Wilson disease was made. The patient was treated with d-penicillamine (250 mg) in a dose of one capsule that was increased to 500 mg per day for seven days along with a zinc sulfate capsule (500 mg) three times a day. He was also given triphenhexyldyl (2 mg) twice a day and pyridoxine, 20 mg orally. The patient was administered miltefosine (50 mg) capsules twice a day for 28 days after meals. After one month of therapy, no LD bodies were found in a splenic aspirate. After this treatment, he became afebrile and hemoglobin levels and other laboratory parameters returned to normal levels. His dystonic movements were reduced considerably and he was able to walk. His rigidity also decreased. He was asked to report after one month. At a one-month follow-up, he showed an improved condition. All parameters including renal and hepatic profiles were normal. There was no albumin in the urine. He did not have fever or hepatosplenomegaly. He was advised to continue treatment with d-penicillamine, zinc sulfate, triphenhexyldyl, and pyridoxine for the rest of his life. Unfortunately, the patient was lost to follow-up after three months.

DISCUSSION

This is one of the rare presentations where a case of VL was associated with Wilson disease. He most probably had Wilson disease and contracted VL later because he lived in a region endemic for VL. The patient had characteristic features of VL such as fever, hepatosplenomegaly and pancytopenia, as well as those of Wilson disease such as tremor, dysphagia, dysarthria, choreo-athetoid dystonic movements, and psychosis. Hepatosplenomegaly is common to both diseases.

Various drugs have been used to treat VL, but because of increasing incidence of unresponsiveness to sodium antimony gluconate and toxicity of pentamidine isethionate, amphotericin B (a polyene antibiotic) that is mainly used as an antifungal agent, is the drug of choice for treating VL. A new oral drug, miltefosine (hexadexylphosphocholine), is now available in India, and phase III and IV trials of this drug were conducted at our research institute.8 Miltefosine is an antineoplastic agent that has been used as a topical application for metastasis of breast cancer. It showed a cure rate of 95% with few side effects such as loose motion and vomiting.

Wilson disease is an uncommon disease. Diagnosis is based on at least two of the following criteria: 1) detection of KF rings on slit lamp examination of the cornea, 2) typical neurologic symptoms, 3) low serum ceruloplasmin level (< 25 g/L), 4) increased excretion of copper > 100 μg/24 hours in urine and 5) a copper level of 200 μg/g of dry weight of liver. Increased plasma levels of ceruloplasmin, an α2 globulin containing 95% of total serum copper, can be increased due to primary (genetic) elevation and secondary causes such as estrogens and pregnancy. Decreased levels can be seen in primary (genetic) deficiency and also due to secondary causes such as dietary copper deficiency, Wilson disease, and Menge’s disease (an autosomal X-linked disorder). Low levels of ceruloplasmin are also seen in protein-losing enteropathy and in nephrotic syndrome. Early detection and treatment protects patient from devastating organ damage.

Siblings of the patients with Wilson disease have a one in four risk of developing the disease. The main treatment consists of reduction in dietary copper to less than 1 mg/day by reducing intake of copper-rich foods (liver, mushrooms, chocolate, nuts, shellfish) and administration of copper-chelating agents such as oral d-penicillamine (0.75–1.5 g/day in adults and 20 mg/kg body weight in children). Pyridoxine, 25 mg, should be given to prevent anemia. Oral zinc therapy leads to storage of metallothionein (bound copper in the mucosa of the gut) and to the excretion of copper in the stool. Newer approaches to therapy include tetrathiomolybdate for neurologic disease and a combination of trientine and zinc with mild-to-moderate hepatic failure.9,10

Until recently, little research has been conducted on drug interactions between penicillamine and miltefosine. However, penicillamine can cause leukopenia and anemia, which are characteristics of VL. This can lead to difficulty in patient management.

Patients with VL and Wilson disease require life-long treatment, which increases costs of diagnosis and patient management. Sodium antimony gluconate and amphotericin B are provided by the Government of India at primary health centers for treatment of VL. Recently, miltefosine has been included in the VL elimination program at the pilot level in a few districts in Bihar, India. However, treatment for Wilson disease is not provided by the government except in a few hospitals. Thus, treatment for such a combination of diseases is currently beyond the means of people of low socioeconomic status.

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