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Recurrent bleeding and bulbar myasthenia-like symptoms as the initial presentation of Wilson's disease: a case report

[1]N Prasun *MD*, [1]M Bagchi *MD*, [2]A Joseph *MBBS*, [1]S Pal *DM*, [3]S Ghosh *MD*, [4]S Mukherjee *MS*, [1]AK Senapati *DM*, [1]SK Das *DM*

[1]Department of Neurology, [3]Department of Radiology, Bangur Institute of Neuroscience, Kolkata; [2]Department of Medicine, Institute of Post-Graduate Medical Education and Research, Kolkata; [4]Department of Ophthalmology, Regional Institute of Ophthalmology, Kolkata, West Bengal, India

Abstract

Wilson's disease, an autosomal recessive disorder of copper metabolism, is usually associated with hepatic or neuropsychiatric manifestations. This is to describe a case of Wilson's disease presenting with recurrent bleeding and bulbar myasthenia-like symptoms. A 12 year old Hindu girl presented initially with recurrent bleeding manifestations such as epistaxis, hematemesis and melaena and followed by swallowing difficulty with fatigability after 2 years. The bleeding was attributed to thrombocytopenia initially and the swallowing difficulty remained undiagnosed as tests for myasthenia gravis were negative. Four years later, the patient developed nasal intonation of the voice with fatigability followed by a decline in scholastic performance. The patient was evaluated in our institute and subtle extrapyramidal signs in the form of asymmetric appendicular dystonia and bradykinesia were noted. Clinical evaluation, laboratory and radiological investigations led to the diagnosis of Wilson's disease. The cause of bleeding was most likely a defect of platelet function. No other cause of her bulbar myasthenia-like symptoms was evident. This case illustrates that in all patients of Wilson's disease with bleeding, a platelet function defect needs also to be considered. In cases of bulbar myasthenia-like symptoms where the diagnosis is not clear, Wilson's disease should be considered in the differential diagnosis, if there is hepatosplenomegaly.

INTRODUCTION

Wilson's disease is an autosomal recessive disorder of copper metabolism. The majority of patients of Wilson's disease (WD) present with either hepatic or neuropsychiatric manifestations.[1] Although haematologic manifestations (haemolytic anemia, thrombocytopaenia and leukopaenia) are described in Wilson's disease, they are less emphasized. Myasthenia-like symptoms in Wilson's disease have been attributed to D-penicillamine therapy. We present a case of Wilson's disease where recurrent bleeding manifestations followed by bulbar myasthenia-like features were the only presenting features for years, leading to delay in diagnosis.

CASE REPORT

A 12-year-old Hindu girl, born of a non-consanguineous marriage, presented initially with purpuric spots, epistaxis, haematemesis and melaena. Investigations showed low platelet count of 40,000/c.mm with a normal bone marrow study. An initial diagnosis of idiopathic thrombocytopenic purpura (ITP) was considered and the patient received a course of IVIG followed by oral steroids leading to remission. One month later, platelets became normal and remained between 150,000 to 294,000/c.mm over four years. After that she again developed recurrent episodes of epistaxis and gum bleeding, for which no local or systemic cause could be found. There was no history of any incriminating drug intake.

After about two years of initial illness, the parents noticed insidious onset and progressive swallowing difficulty which was predominantly for liquids, associated with fatigability. Repetitive nerve stimulation test to look for myasthenia gravis did not show a decremental response and the acetylcholine receptor antibody titer was also negative. For the next one year, these symptoms persisted along with recurrent bleeding manifestations. Later, the patient developed nasal intonation of voice and gait abnormality with a

Address correspondence to: Prof. SK Das, DM, Prof. and Head, Department of Neurology, Bangur Institute of Neuroscience, 52/1A, S. N. Pandit Road, Kolkata-70002, India. Phone No. 0091-33-2223-8030 (O), Fax: +91-33-24751799, E mail: das_sk70@hotmail.com

tendency to recurrent falls. During this period there was also a decline in her scholastic performance and she was referred to our institute.

Cognitive testing revealed mild impairment of concentration and visuo-constructional ability. On physical examination, Kayser-Fleischer rings were present, along with firm non-tender mild hepatomegaly and splenomegaly, jaw opening dystonia, dysarthria and nasal intonation of voice with fatigability. Extraocular movements showed impaired vertical pursuits especially on downward gaze and impaired convergence. Other positive findings include decreased palatal movements, mild antecollis (10 degrees), mild rigidity and dystonia of upper limbs with some asymmetry and bradykinesia with normal power and reflexes. Gait showed occasional start hesitancy and decreased arm swing on the right. Postural instability was present.

Investigations at our institute showed a normal complete blood count except for the platelet count of 90,000/mm^3. The peripheral blood smear revealed normal red blood cell and leukocyte morphology. The morphology of platelets was typically normal, with varying numbers of large platelets. The size of the spleen as measured by sonography was 12 cm along its longer dimension and the liver extended 5 cm below the right costal margin. Platelet function studies showed reduced aggregation with ADP, suggestive of a non-specific disorder of platelet function. The prothrombin time, bleeding and clotting times along with liver, renal and thyroid function studies were normal. Bone marrow examination showed cellular marrow with increased megakaryopoiesis and erythropoiesis and normal leukopoiesis (Figure 1). Her serum ceruloplasmin level was low at 4.42 mg/dl (normal 20-40 mg/dl) with a mildly elevated 24-hour urinary copper excretion at 68.60 μg/24 hours (normal 20-50 μg/24 hours), consistent with a diagnosis of Wilson's disease. Abdominal ultrasound showed hepatosplenomegaly without evidence of portal hypertension. Brain MRI showed bilateral symmetric hyperintensities in long TR sequences in the basal ganglia, thalamus, midbrain, and pons. (Figure 2).

Treatment was started with zinc sulphate 200 mg (50 mg of elemental Zn) thrice daily along with symptomatic treatment of dystonia with trihexyphenidyl and clonazepam. The bleeding symptoms improved along with motor symptoms after the treatment but the hepatosplenomegaly persisted.

DISCUSSION

This patient with WD had two main symptoms initially - recurrent bleeding manifestations and later swallowing abnormality associated with fatigability. Initially the recurrent bleeding was attributed to ITP. Platelet count remained normal for about four years. The initial response of thrombocytopaenia to steroid and IVIG can possibly be due to immune-mediated thrombocytopenia associated with Wilson's disease. Thrombocytopaenia in Wilson's disease

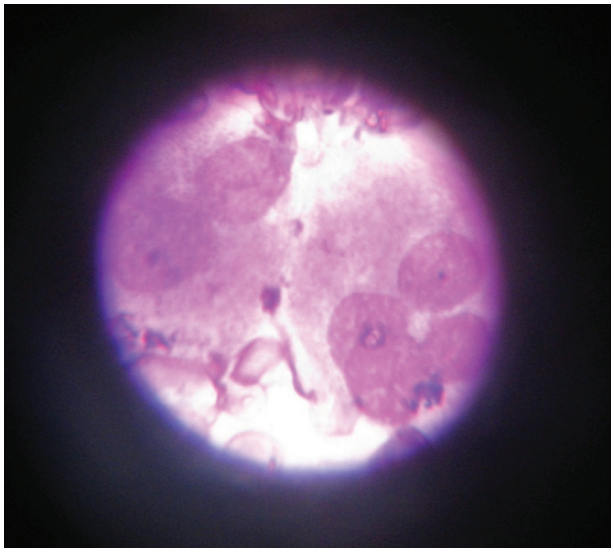

Figure 1. Bone marrow showing increased megakaryopoiesis and erythropoiesis.

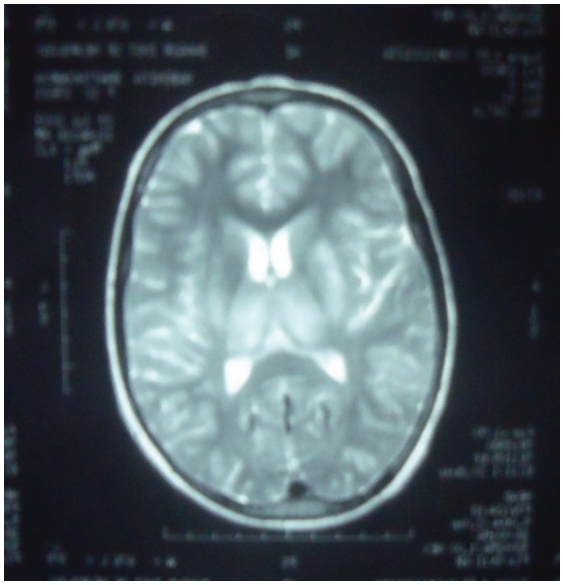

Figure 2. T2-weighted brain MRI showing bilateral symmetrical hyperintensities in the basal ganglia and thalamus

can also be due to hypersplenism.[2] In chronic liver disease, such as may occur in Wilson's disease, there can be both thrombocytopenia and platelet function abnormality similar to this case.[3,4] Platelet function abnormality can be due to decreased glycoprotein 1b on the platelet wall and decreased signal transduction abnormality along with decreased shape change.[4,5]

Because of prominent bulbar signs and symptoms with prominent fatigability, myasthenia gravis of bulbar variety was considered a possibility. In laboratory experiments, copper may produce neuromuscular blockade by acting mainly on the presynaptic nerve terminals to decrease the release of acetylcholine.[6] Other studies show a close relationship between the divalent metal ions binding site in the motor end plate and the site of cholinesterase activity and the acetylcholine receptor.[7] The myasthenia-like symptoms in our patient may be related to disturbance of copper producing neuromuscular blockade.

We report this case of Wilson's disease because of its two unusual presenting features - recurrent bleeding and bulbar myasthenia-like symptoms. We propose that in all cases of recurrent bleeding and bulbar myasthenia-like symptoms, a differential diagnosis of Wilson's disease should be considered if there is hepatosplenomegaly.

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