Case Report

Adult Type 3 Gaucher Disease as Manifestation of R463C/Rec Nci I Mutation: First Reported Case in the World Literature

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Abstract

Gaucher disease is the most common lysosomal storage disorder. It is autosomal recessive in nature and results from mutations in the GBA gene coding for acid beta glucosidase. It is classified into three types based on CNS involvement and its severity. Type 3, or chronic neuronopathic Gaucher disease, generally has an onset in childhood and by definition, includes all patients with any form of neurologic involvement who have survived the first few years of life. Here we present a 36 year old male patient presenting with hip pain showing bilateral avascular necrosis of femoral head with massive splenomegaly and on evaluation, showed mental retardation, seizures, bilateral vertical and horizontal gaze palsies and eventually turned out to be type 3b Gaucher disease. This is the first case of Type 3 Gaucher disease being reported from India with mutation analysis and only case of Type 3 Gaucher disease in world literature showing R463C/Rec Nci I mutation.

Introduction

The name ‘Gaucher’ was coined by Brill in 1905.¹ Gaucher disease is a lysosomal glycolipid storage disease. Type 3 Gaucher disease is a sub-acute neuronopathic form and accounts for 5% of all Gaucher disease cases.² The case we are presenting is type 3b Gaucher disease with relatively late age of onset. Patient had neurological signs, bone marrow involvement, massive splenomegaly, and skeletal involvement resulting in avascular necrosis of bilateral femur. The diagnosis was made by demonstration of Gaucher cells in Bone marrow, enzyme estimation and DNA analysis showing mutation in the GBA gene.

Case Report

A 36 year old male from Shimla, Himachal Pradesh, India an employee in Public works department presented to the department of Orthopedics at Indira Gandhi Medical College, Shimla with 8 month history of pain in left groin and thigh followed 2 months later by pain in right groin and thigh. Imaging studies showed bilateral avascular necrosis of femoral head. Patient was examined and showed massive splenomegaly on examination. Patient was referred to department of medicine to rule out leukemia/lymphoma as cause for avascular necrosis.

A detailed history revealed that patient was a known case of generalized tonic clonic seizure disorder since the age of 24 years; was on antiepileptics for the same. He was a school dropout and had been operated for bilateral juvenile cataract. There was no history of steroid use, chemotherapy, trauma, recurrent infections, bleeding tendency or any history suggestive of sickle cell disease. Family history was negative for any hereditary disease. He was not born of a consanguineous marriage and siblings were all normal.

General examination revealed reduced height (152 cm), pallor, and kyphoscoliosis. His pulse, BP, and respiratory rate were normal. On systemic examination, patient had barrel shaped chest with pectus carinatum. Air entry was normal with normal vesicular breath sounds bilaterally. Patient had massive splenomegaly (14 cm below costal margin). The spleen was firm in consistency and non tender. Patient was not aware of the abdominal lump. There was no hepatomegaly. Ophthalmological examination revealed a visual acuity of 6/8 and 6/24 (aided), and bilateral aphakia. There was bilateral lateral and vertical gaze palsy and low mini-mental score (22/30). Rest of the neurological examination was normal. There was shortening of left lower limb with restricted hip movements bilaterally, left more than right. Cardiac examination was normal.

Hb was 9 g/dl, total leukocyte count 3800/cu.mm, and platelets were adequate. Liver function tests, kidney function tests, electrolytes, serum calcium, phosphorous and ECG were normal. X-ray spine revealed diffuse osteopenia with kyphoscoliosis. CT abdomen showed markedly enlarged spleen, measuring 20 cm in craniocaudal extension with altered signal intensity and multiple hypodense areas of varying sizes, which were possibly splenic infarcts. Liver was normal in size and no lymphadenopathy was found. Pulmonary function test revealed mild restrictive defect. MRI brain, ECHO and CT thorax were normal. MRI hip joints (Figure 1) showed bilateral avascular necrosis of femur proximally.

Bone marrow examination was done to rule out myeloproliferative disease, which revealed a cellular marrow with an M: E ratio of 2.5:1. There were large cells with one – two dark eccentrically placed nuclei with pale cytoplasm having fine granular wavy fibrils – features consistent with Gaucher cells. The cells were PAS positive and negative for Sudan black. Plasma cells were 1 %. No parasite or granuloma was found. Leukocyte acid glucosidase activity assay revealed low glucosidase activity at 2.26 mmol/h/mg protein at pH 5. Patient’s galactosidase activity was also found to be low. DNA analysis by restriction digest and direct sequence technique to detect DNA sequence mutation on patient’s GBA gene revealed two mutations, Rec Nci I and R463C mutation on patient’s GBA gene.

Patient was diagnosed as a case of type 3b Gaucher disease.
Classically, Gaucher disease has been diagnosed by demonstrating storage cell, the Gaucher cell. However, diagnosis is best made by detecting low beta glucosidase activity in leukocyte, though not yet routinely used at every centre. PCR is useful in detecting the mutations. Mutation analysis has considerable predictive value with respect to disease prognosis.1

Treatment includes supportive measures like splenectomy, orthopedic interventions and specific therapy. Specific therapy is in the form of enzyme replacement, which is costly as well as not widely available. Allogenic bone marrow transplantation and Chaperone therapy and gene transfer are the latest therapeutic options.1,2

Our patient, in addition to glucocerebrosidase deficiency, also had galactosidase deficiency. Multiple glycosidase deficiencies have been proposed as the reason for the difference between infantile and adult Gaucher disease.3

Till now the cases of Gaucher disease reported from India are mainly type 1 cases. Manjeet Kaur et al.4 identified 13 cases of Gaucher disease in Delhi and Bombay by enzyme assay in leucocytes. All cases except one belonged to type 1 (hepatosplenomegaly), while one case was of type 2 (neuronopathic).

The largest series of 7 cases to be published in India seen in one particular community is amongst the Mappila Muslims of Malabar all were type 1 (Adult).5 Diagnosis was based on the clinical manifestations and demonstration of Gaucher cells in the bone marrow. Enzyme assay and DNA analysis were not done.5

Our patient has been fully investigated including DNA analysis. Also the mutation found R463C/Rec Nci I has not been seen manifesting as Type 3 Gaucher disease in any case till date. The genotype to phenotype correlation was studied in 46 British and Irish patients.6 Only 2 patients were found with the R463C/Rec Nci I mutation as in our patient, but both had Type I childhood type Gaucher disease.6 Our case had the phenotypic presentation of Type 3 Gaucher disease with extensive neurological and visceral involvement instead. The possible explanation for which may be multiple glycosidase deficiencies found in our patient i.e. glucocerebrosidase and galactosidase deficiencies both.

Discussion

Gaucher disease is a human genetic disease due to mutation in the GBA gene on chromosome 1q21, that codes for an enzyme glucocerebrosidase found in the lysosome. Glucocerebrosidase breaks down and regulates glucocerebroside, which is a normal part of the cell membrane. In people with Gaucher disease this fat accumulates in the reticuloendothelial cells of liver, spleen and bone marrow causing them to lose their normal functions.1

Four common mutations (N370S, L444P, 84GG, and IVS2) account for approximately 95% of all non functioning Gaucher genes.1 This uncommon disease is common in the Ashkenazic Jews where the incidence is 1 in 855.

Three forms of Gaucher disease are:

- Type 1: Mild form (95%) without neurological involvement common in Ashkenazic Jews.1,2
- Type 2 (infantile form): The acute neuronopathic form that has malignant course with severe neurologic involvement and death before the age of 2 years usually by respiratory compromise.1,2
- Type 3 (juvenile form): Has a much benign course and 3 subtypes with varying visceral and neurologic involvement. Type 3b has aggressive visceral and skeletal disease, but neurologic manifestations mainly limited to horizontal supranuclear gaze palsy.2

The most debilitating is bone involvement clinically apparent in 20%.1 Avascular necrosis and bone crisis are the usual complications. Cytokines (IL, TNF) released by Gaucher cells and glucocerebroside have been implicated in the pathogenesis of increased bone resorption and infarcts.

Neurological abnormalities are seen, the most common being horizontal gaze palsy,1,5 in addition to seizures, mental retardation, dementia, bulbar signs and ataxia.

References