Gaucher Disease in Two Siblings

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Introduction

Gaucher disease (GD) is the most common enzyme deficiency disorder among the group of approximately 50 inherited lysosomal storage disorders [1]. The underlying cause is a deficiency of glucocerebrosidase, a lysosomal hydrolase involved in the stepwise degradation of complex glycosphingolipids. Gaucher disease is classified, based on clinical characteristics into: Type 1-Non Neuronopathic, Type 2-Acute Neuronopathic and Type 3-Chronic Neuronopathic. Type 1 disease is the most prevalent and has a wide spectrum of presentation. We report a rare presentation of two siblings diagnosed as Type 1-Gaucher disease at ages of two years and ten months respectively.

Case Report

A two year old female child presented with progressive distension of the abdomen associated with failure to thrive. She had achieved her developmental milestones normally. On examination she was pale, irritable with a large distended abdomen. Her weight was 8 kilograms and a height of 83 cms. General exam did not reveal any lymphadenopathy, pedal oedema, icterus or rash. Systemic exam was positive only for massive hepatosplenomegaly. No neurological deficit was noticed. Her haemoglobin was 8.7 gm % and platelet count 45000/cumm. Peripheral blood smear (PBS) was suggestive of microcytic hypochromic anemia with thrombocytopenia. Blood tests were carried out for leishmania antibody, TORCH titers, malaria parasite, hepatitis B surface antigen and all were negative. She was investigated to rule out leukemias, lymphoma, and malignancies by way of bone marrow aspiration and liver biopsy which were reported as reactive and chronic hepatitis respectively. The suspicion of a storage disorder got strong at this point and the child was tested for blood glucocerebrosidase which was found to be absent in her. The asymptomatic younger sibling aged ten months was also examined and found to have hepatosplenomegaly with absent glucocerebrosidase levels in blood. Based on the

absence of the enzyme glucocerebrosidase in blood, the children were diagnosed as Gaucher Disease-Type I (Non neuronopathic). They are being managed with blood transfusions and are on regular follow up (Fig. 1).

Discussion

Gaucher disease is a panethnic disorder inherited in an autosomal recessive way. The prevalence of symptomatic disease is 1:100,000 [2]. Nonneuronopathic GD is the most frequent form (94%) and is differentiated from the acute neuronopathic (1%) and chronic neuronopathic (4%) forms by the absence of central nervous system involvement [3].

Clinical expression is remarkably variable in the Type 1 or the non-neuronopathic form. Disease progression is unpredictable and can occur at any age. At presentation the patients may bruise easily owing to thrombocytopenia, chronic fatigue secondary to anemia, hepatomegaly with or without deranged liver function tests, splenomegaly and bone pains. The skeletal system involvement manifests as bone pains, osteonecrosis, bone marrow infiltration with Gaucher cells, osteopenia, lytic lesions, sclerosis, Erlenmeyer flask deformity-bone

Fig. 1 : Two siblings with Gaucher disease

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remodeling failure which occurs regardless of disease severity [4]. The visceral manifestations are in the form of splenomegaly followed by hepatomegaly. Hematological manifestations take the shape of anemia, thrombocytopenia, neutropenia, pancytopenia and coagulopathy. In the classical acute neuronopathic form, symptoms are characterized by an onset within the first six months and rapid progression. Typically all these patients die within the first three years. Prominent neurological manifestations are spasticity, persistent retro flexion of the head, strabismus, oculomotor apraxia, trismus, dysphagia, stridor and exaggerated deep tendon reflexes [5]. Patients of chronic neuronopathic disease may have an onset during childhood with hepatomegaly, skeletal lesions and development of slowing of the conjugate horizontal saccadic eye movements. Neurological degeneration results in death in the second or the third decade of life.

The diagnosis of Gaucher disease rests on the assay of glucocerebrosidase activity in peripheral blood leucocytes or cultured fibroblasts. In general, Gaucher patients have an enzyme activity that is $\leq 30\%$ of normal activity. In some patients the diagnosis may first be suspected after a bone marrow aspiration study for the evaluation of chronic anemia, thrombocytopenia, and/or splenomegaly which demonstrates Gaucher cells. However, a bone marrow aspirate is not the final diagnostic test because misdiagnosis of Gaucher disease may occur in patients with hematological malignancies, e.g. leukemia, Hodgkin's disease [6]. Definitive diagnosis of Gaucher disease should be based on reduced glucocerebrosidase activity [7].

Till date more than 300 mutant alleles have been identified. Presence of at least one N370S allele is associated with Type 1 disease and excludes neuronopathic involvement, while homozygosity for L444P generally predicts Type 3 disease. An important role for genotyping relates to screening and genetic counselling of the patients family. The identification of carriers can be achieved by enzymatic assay and molecular studies. Testing should be offered to all family members, keeping in mind the great heterogeneity of the disease process, where even asymptomatic individuals may have a relative enzymatic deficiency. Prenatal diagnosis is available by determination of enzyme activity in chorionic villi and amniotic fluid cells.

Some Gaucher disease biomarkers have been

identified which include chitotriosidase and CCL18/ PARC. Other biochemical markers are angiotensin converting enzyme (ACE) and tartrate resistant acid phosphatase (TRAP).

Treatment of Gaucher disease is supportive in the form of blood transfusions, hematinics and orthopaedic procedures. Specific therapy is provided only by the way of replacing the enzyme glucocerebrosidase. Enzyme replacement therapy (ERT) with intravenous recombinant glucocerebrosidase (imiglucerase, cerezyme) is the preferred treatment for symptomatic patients with non neuronopathic (Type I) Gaucher disease [8]. The initial ERT dose is 60-120 units/kg body weight every two weeks. The same dose is administered till therapeutic goals are achieved and no adjustment of the dose is done for six month period. The other modalities of treatment are the administration of Miglustat which is a new substrate reduction therapy approved in 2003 for those patients who cannot tolerate ERT. Bone marrow transplant is a procedure with high morbidity and mortality. Other modalities under investigation are gene therapy which holds promise.

Conflicts of Interest

None identified

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