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Case Report

Internal Medicin Section

Type 1 and Type 3 Gaucher Disease in Two Siblings in A Family: 2 Unusual Case Reports

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ABSTRACT

Gaucher disease (GD) is an autosomal recessive disorder, characterized by lack of acid β-glucosidase (glucocerebrosidase) enzyme resulting in accumulation of glucosylceramide in different organs. It is common in Ashkenazi Jews but rare in India. Around five hundred cases are identified and diagnosed in India. We are reporting two interesting cases of type 1 non-neuropathic and type 3 juvenile subacute neuropathic variant of adult Gaucher disease in two of three siblings in a family.

Keywords: Gaucher disease, Glucocerebrosidase, Lysosomal storage disorder, Sibling

CASES

Case -1

A 17-year-old female born to parents of non-consanguineous marriage was referred to us with easy fatigability, respiratory distress of one month duration and dragging sensation in left side of upper abdomen for three years. History revealed primary amenorrhea, stunted growth and recurrent respiratory tract infections requiring hospitalizations during the past two years. There was no history of jaundice, rash, joint pains, bone pain or bleeding from gastrointestinal tract. She had received five units of blood transfusions in the past three months. She had a body weight of 27kg and height of 106cm. She was afebrile, pale, and had hepatomegaly and massive splenomegaly (4cm and 17cm below the costal margins respectively). Examination of other systems was noncontributory. Laboratory investigations revealed hemoglobin 8.2 gm%, WBC count 2300/cmm (Neutrophil -50%, Lymphocyte - 32%, Monocyte -4%, Eosinophil -14%), Platelet-80 lakh/cmm. Hemoglobin electrophoresis was normal. Liver function tests demonstrated total bilirubin -1.3 mg% (conjugated-0.4mg%) , albumin: globulin - 3.2:3.7, SGPT - 35 IU/ml, SGOT - 49 IU/ml, alkaline phosphates -726 IU/ml. Prothrombin time was 12 s. Blood urea, serum creatinine, sodium, potassium, calcium, thyroid and lipid profile were within normal limits. Ultrasonography showed hepatosplenomegaly and no abnormality was detected in X-ray of chest and large and small joints. Serum FSH (5.03 mIU/ml) and LH (11.12 mIU/ml) were within normal range. For evaluating pancytopenia with hepatosplenomegaly a bone marrow (BM) aspiration and trephine biopsy was done. BM smear showed normoblastic marrow with normal megakaryocytic and normal erythroid leukocyte ratio. Histopathological examination of bone marrow trephine smear demonstrated large cells with small irregular nuclei and abundant vacuolated cytoplasm suggestive of Gaucher cells. Acid β-glucosidase activity was estimated and found to be < 25% of normal. On basis of age, mode of presentation and evidence on bone marrow with enzyme deficiency, a diagnosis of type 1 GD was made. To combat pancytopenia, repeated respiratory infections and mechanical discomfort of huge splenomegaly, splenectomy was carried out.

The spleen measured 20cms in its great axis and weighed 1270g; cut surface showed pale grayish and brownish areas and histopathological study revealed infiltration of red pulp with histiocytes having abundant pale acidophilic cytoplasm, suggestive of GD.

Case - 2

Her 20-year-old elder brother, apparently asymptomatic, but inattentive, presented with pallor and hepatosplenomegaly (liver 3cm, spleen 5cm below costal margin). On examination, there was strabismus. Hemoglobin -7gm%, WBC-3000/cmm, Neutrophil - 62%, Lymphocyte - 30%, Monocyte - 2%, Eosinophil - 6%, platelet-70,000/cmm. Other relevant investigations including serum ceruloplasmin, 24h urinary copper excretion were normal. Bone marrow aspiration was done and Gaucher cells were demonstrated, with low acid β-glucosidase activity. Six months later, he presented with dementia, abnormal aggressive behaviour which needed psychiatric consultation. In next three months he suffered three episodes of convulsion. Computed tomography, EEG reports revealed no abnormality. He was diagnosed as a case of type 3 GD which has highly variable manifestations in the CNS and viscera.

The 14-year-old third sibling was also examined and he did not show any evidence of GD on clinical and laboratory examination. Their parents were screened for the disease and both of them had low enzyme activity (acid β-glucosidase).

Follow up- Body weight of the girl child was increased by 6kg within 3 months of operation, she experienced menarche six months after splenectomy and never required hospitalization in next 2 years follow up care but her brother needed constant psychiatry treatment support.

DISCUSSION

Gaucher disease is a very rare genetic disease; occurring in 1 in 50,000 to 100,000 people in the general population. About 1 in 100 people in the United States are carrier of type 1 GD and in Ashkenazi Jews carrier state is 8.9% while the birth incidence is 1 in 450 [1]. Three major types have been delineated according to presence or absence of neurological manifestations. Type 1(non-neuropathic) is the commonest variety; neurological manifestations are absent and have a bimodal presentation, with peaks at 10-15 y and around 25y. Younger patients present with hepatosplenomegaly, features of cytopenia and older ones with chronic bone disease and are compatible with long life [2]. Type 2 (infantile, acute neuropathic) is the severe form with extensive visceral and brain involvement, seizure, spasticity, usually dies before the 3rd birthday. Type 3

(juvenile or Norrbotten form) is chronic milder variety, having fewer neurological problems, usually presents with organomagaly, eye abnormality, skeletal irregularities, seizure etc. They may live early teen or adulthood. Both type 2 and 3 are found in 1 in 1, 00,000 population and has no ethnic predilection [1].

The first case presented to us with pancytopenia massive hepatosplenomegaly, stunted growth and increased propensity for infections which was similar to the case series of JJ Sheth et al, who reported that type 1 disease clinically presents with splenomegaly (95%), hepatomegaly (87%), thrombocythemia (50%), anaemia (40%), growth retardation (34%), radiological bone disease (27%), bone crisis (9%) and bone pain (27%) [3]. Diagnosis is confirmed by measurement of enzyme activity in peripheral blood leucocytes (gold standard) or from cultured skin fibroblasts or other nucleated cells. Demonstration of Gaucher cells in bone marrow is sufficient for the diagnosis, where enzyme activity cannot be measured [4].

Vartika et al., studied spectrum of mutation pattern in 24 Indian patients from 20 families, showing presence of L444P, N370S, IVS2 and D409H and 55 Del mutations in approximately 50% of the patients. L444P was the commonest, followed by D409H in their study [5]. The disease severity and its various clinical courses depend upon the nature of the mutation in the glucocerebrosidase gene and its genotype/phenotype correlations [6].

Enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) are the backbone of the management. Partial splenectomy may be the first treatment option in pediatric age group which improves hematological status and growth [7]. Advances in the management of this neglected, rare disorder continue to be hindered by high cost of therapy.

Perhaps the largest series from one single community reported from India was by Feroze et al., who identified seven cases from a Mappila Muslim community in Malabar [8].

Being a rare disorder worldwide and in India here we report two cases in a family with typical presentation which were confirmed by histopathology and enzyme analysis.

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