Case Report

Gaucher's disease — diagnostic value of bone marrow examination and genetic study

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Gaucher's Disease is a rare Genetic Autosomal Recessive Lysosomal Storage disorder caused by inherited deficiency of acid-ß-Glycosidase (Glucocerebrocidase-GBA) which results in glycosphingolipid Glucosylceramide to accumulate within lysosomes of Macrophages[12]. Out of Three types of this disease type I is most common form of the disease and it does not involve CNS and can be present at Adulthood. In Present case 22 years old Female presented with weakness and abdominal fullness and pain. Hemogram shows Pancytopenia and USG revealed Hepatosplenomegaly. On Bone marrow examination Gaucher's Cells found and Gaucher's Disease (Type 1) diagnosis was made. Treatment of this disease is enzyme supplementation and Bone marrow transplantation.

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***Key* words : Gaucher's disease, bone-marrow examination, genetic study.**

Gaucher's Disease named after the French Doctor Philippe Gaucher, who originally described it in 1882. Storage of glucocerebroside was first recognized by Epstein in 1924 This disease presents with Symptoms of Pancytopenia, Hepatosplenomegaly, skeletal disorders, painful bone lesions, neurological complications, lymphadenopathy, and yellow deposition on the sclera[14] and can be diagnosed by Bone Marrow examination, Enzyme estimation and Definate diagnosis by Genetic Testing. Treatment of this disease is Enzyme Replacement therapy (ERT) and Bone marrow Transplantation[14].

Case Report

A 22 year old female came to OPD with complains of weakness, Abdominal Pain. No any other complains were present.

Examinations — The patient's Vital signs were within normal limits. There was pallor, Hepatosplenomegaly. There was no lymphadenopathy, Sternal tenderness or any skeletal abnormalities.

Investigations — Routine Hemogram shows Hb : 5.4g/dl ,Total RBC count : 2.85 mil./cmm Total Leukocyte Count: 2500/cmm, Diffential Count P_{52} L_{42} E_{03} M_{03} B_{00}, ESR : 65 mm/ 1st hour, Platelet count : 1,10,000 /cmm. Her Ferittin was 368 ng/ml and Vit. B-12: >2000 pg/ml, SGPT: 78.52 U/ml, total Billirubin: 0.73 mg%, Direct Billirubin: 0.60 mg%, Alkaline Phosphatase 91.25 IU/ml. Her peripheral smear shows Dimorphic Anemia with Leucopenia and Thrombocytopenia (Pancytopenia). Angiotensin Converting Enzyme (ACE) was 118.0 u/l.

Her USG examination shows Liver enlargement of 18 cm with Splenic Enlargement.

From the history, clinical examination and investigations it was evident that patient is suffering from Pancytopenia with high ESR and Hepatosplenomegaly. So Bone-Marrow aspiration examination was planned.

On Bone marrow examination many large Histiocytic cells having eccentric or centrally placed nuclei with fibrillary or striated pattern pale blue to grey 'crumpled cigarette paper' like cytoplasm. (Gaucher's cells) were present and Gaucher's Disease Diagnosis was made (Fig 1).

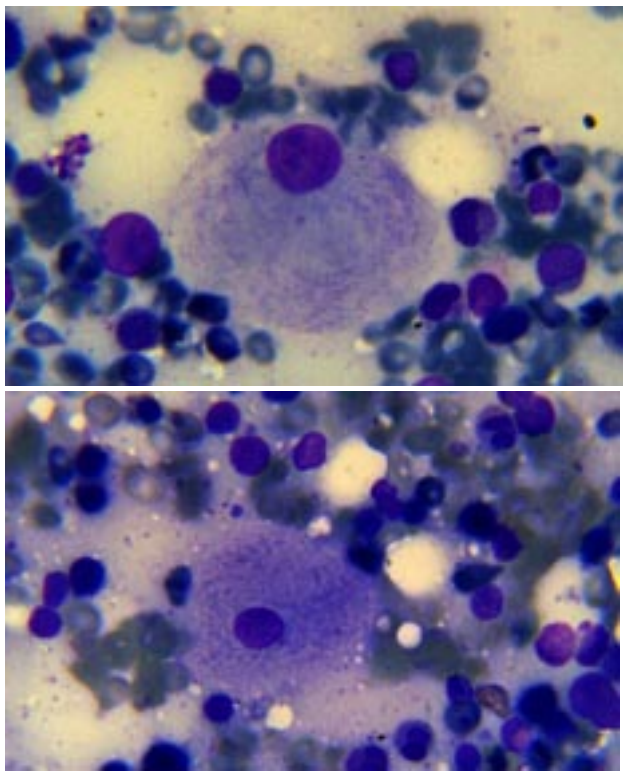

Fig 1 — Gaucher's cell (50x, field's stain)

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Discussion

Gaucher's Disease is a genetic disease and the most common of Lysosomal Storage Disease. It is a form of Spingolipidoses caused by deficiency of acid- ß -glucosidase enzyme which acts on glucosylceramide fatty acid, so there is accumulation of this fatty acid in macrophages. This can collect in Liver, Spleen, Kidneys, Brain and Bone marrow[11].

Epidemiology and Genetic Aspects :

The disease is affecting an estimated 1 in 50,000 to 1 in 100,000 people of the general population[6]. Persons of Eastern and Central European (Ashkenazi) Jewish heritage are at higher risk for the disease with incidence rate of approximately 1 in 500 to 1000[13]. There is inadequate information on the prevalence of this condition in the Indian population due to its rarity in this part of the world[2]. It is Autosomal recessive so mother and father must both pass one abnormal copy of the gene to the child in order for the child to develop the disease[3].

Located on long (q) arm of chromosome 1, GBA gene codes for production of enzyme Beta glucocerebrocidase[4]. However, the mutations in this gene leads to reduction in the activity of this enzyme causing toxic level accumulation of the glucocerebrosides in the cells which in turn damages the tissues and organs leading to the onset of characteristic features indicating Gaucher's Disease[3]. Most of these mutations are mis-sense mutation related with variable severity observed in the phenotype of the condition, for example the mutation c.1226A>G (N370S) on the GBA gene is often associated with certain degree of neuro-protection causing Type 1[5]. Whereas the homozygosity for the c.1448T>C (L444P) mutation on the GBA gene presents with neurological symptoms[4]. The complexity of identification and characterization of mutations in the gene of GBA is caused by a great amount of mutated alleles. The existence of a highly homologous psudogene and its location on chromosome 1, a highly gene rich region promotes the presence of complex alleles. Based on the mutations present and the numbers of alleles affected, the disease is classified into 3 major types indicating the variable phenotype and different levels of severity[1]. Each type has been linked to particular mutations:

Type I (Non-neuropathic) (N370S homozygote) most common form and does not involve CNS, Clinical manifestation are heterogenous and can come to attention from infancy to adulthood with median age at diagnosis is 28 years of age , range from very mildly affected individuals to those having rapidly progressive systemic abnormalities[4,12].

Type II (1 or 2 alleles L444P) is very rare, characterized by neurological problems in small children. The enzyme is hardly released into the lysosomes and prognosis is poor: most die before age of 3[3,12].

Type III (also 1-2 copies of L444P, possibly delayed by protective polymorphisms) presents in early child hood and most commonly in the Swedish population from the Norrbottern Region. This group develops the disease somewhat later, but most die before the age of 30[4,12].

Diagnosis

Diagnosis of this disease can be made by presence of Gaucher's cells in Bone marrow, Liver or Spleen Biopsy. The Gaucher's cells are having centrally or eccentrically placed nuclei with fibrillary, striated pale blue 'crumpled paper pattern' cytoplasm[5]. This cells show strong PAS and Tartrate Resistant Acid Phosphatase (TRAP) positivity with diffuse iron staining in cytoplasm[8]. Other key diagnosis is enzyme estimation which is decreased in the patient of this disease. It can be diagnosed by demonstration of deficient Acid- ß - Glucoside enzyme in isolated peripheral leucocytes or cultured fibrocytes. Confirmed diagnosis is made by molecular DNA assay which show mutation in GBA gene on chromosome 1. Mutation types N370S, L444p, 84GG, JVS2+1 and sequence analysis is useful for identifying rare mutant alleles associated with Gaucher's Disease[12]. Only Karyotyping will not be able to identify the array of mutation present[10]. Prenatal Diagnosis is available by determining enzymatic activity or specific mutation in chorionic villi or cultured amniotic fluid cells.

Treatment of this disease is Enzyme Replacement Therapy and Bone marrow Replacement. ERT has remarkable effects on Hepatosplenomegaly and anemia, increased growth velocity in children, weight gain and increased energy levels[7,13]. Treatment of patients with Type 1 with recombinant ß-Glucocerebrocidase (Imuglucerase) results in a decrease in the relative volume of bone replaced by Gaucher's cells and an increase in hemopoeitic and fat cells and decreased cortical bone structure[11].

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