Gaucher's Disease : A Rare Genetic Disorder

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***Abstract*-** Gauchers disease caused by beta glucocerebrosidase deficiency, being the commonest lysosomal storage disorder, is a rare genetic disorder. Presenting features vary depending on the types classified by neuronal involvement.

Treatment mainly is symptomatic. Specific therapy includes enzyme replacement, substrate reduction and bone marrow transplant.

I. INTRODUCTION

Gaucher's disease is the most common lysosomal storage disorder. Mode of inheritance being autosomal recessive, It is caused by deficiency of beta- glucocerebrosidase enzyme (present on chromosome 1) which leads to deposition of glucocerebroside in cells of macrophage-monocyte system in various organs.
It is extremely rare in India and commonly found in Ashkenazi jews.
There are three types of Gaucher's disease depending on CNS (central nervous system) involvement as follows -
Type 1 : Non-neuronopathic form, most common type, seen in childhood or early adulthood
Type 2 : Acute neuronopathic form , presents in childhood, Rapidly progressive and fatal
Type 3 : Chronic non-neuronopathic form, slowly progressive

Other types
-Perinatal lethal form
-Cardiovascular form

Individuals with gauchers have clinical features viz bruising, lethargy, anemia, skeletal involvement, hepatosplenomegaly, Interstitial lung disease, pulmonary arterial hypertension. CNS involvement is in the form of cognitive decline, ataxia, gaze abnormalities and seizures.

II. CASE PRESENTATION

9 year old female child , hindu by religion, born to parents of non-consanguineous marriage was admitted to tertiary care hospital with predominant clinical presentation of abdominal distension, loss of muscle strength, short stature & conjunctival hemorrhage in Right eye. Milestones were normal. The parents also gave history of repeated blood transfusions in the past since the child was 6 month old.
On examination the child was pale, cachexic, abdomen was distended (liver was 5cm palpable below right costo-chondral margin and spleen was 20cm palpable below left costo-chondral margin). CNS examination was normal.

Peripheral blood smear was s/o pancytopenia and bone marrow biopsy was showing histiocytes with abundant granular and fibrillar cytoplasm (charecterstic crumpled tissue paper appearance).

Screening was done by enzyme levels which surprisingly turned out to be normal and the diagnosis was confirmed by genetic testing.
Considering the scenario and findings patient was diagnosed type 1 Gaucher's .
Treatment given: multiple blood transfusions f/b splenectomy.

III. IMAGES

Image 1: Muscle wasting with short stature with distended abdomen.

Image 2: Massive splenomegaly crossing the umbilicus.

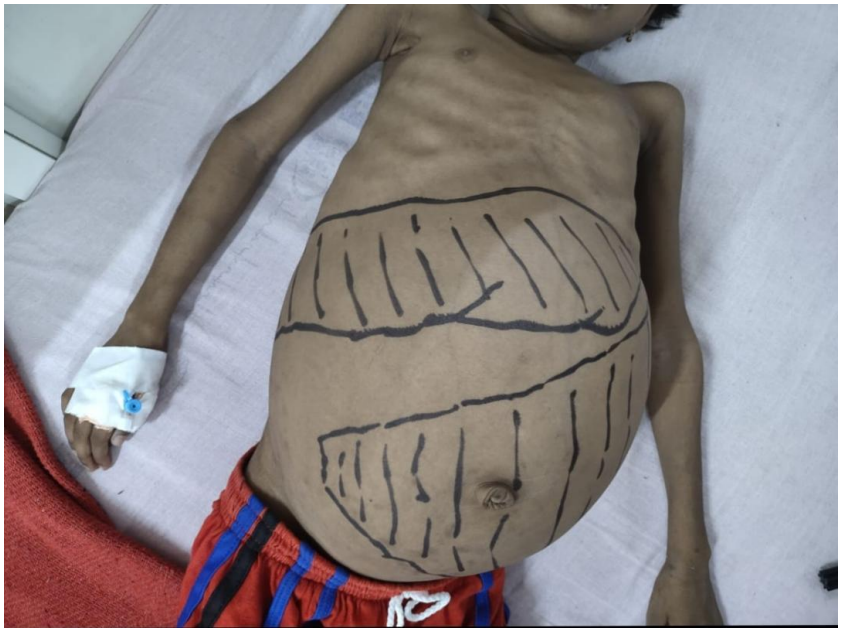

Image 3: Massive Hepatosplenomegaly.

Image 4: Large subconjunctival hemorrhage in Right eye.

Test Performed: Sequence and deletion/duplication analysis of the *GBA* gene
Reason for Referral: Clinical features of disease

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Pathogenic sequence variant and sequencing variant of uncertain significance detected.
No reportable copy number variants (CNV) detected.
Clinical and biochemical correlation is required.

Relevant Findings and Interpretation

Sequence variants:

Classification	Gene	Exon/ Intron	DNA Change	Protein Change	Zygosity	Inheritance	OMIM	Associated Disease
Pathogenic	*GBA*	11	c.1448T>C	p.Leu483Pro	Heterozygous	Autosomal Recessive	606463	Gaucher disease
Uncertain Significance	*GBA*	12	c.1603C>A	p.Arg535Ser	Heterozygous	Autosomal Recessive	606463	Gaucher disease

***GBA* c.1448T>C (p.Leu483Pro) - Pathogenic.** The c.1448T>C (p.Leu483Pro) missense variant results in the substitution of the leucine codon at amino acid position 483 with a proline codon. This variant, also known as p.Leu444Pro, is a common *GBA* pathogenic variant and is frequently identified in individuals with type 2 or 3 Gaucher disease (PMID: 10649495, 10796875, 20301438). The highest population frequency of this allele in gnomAD is 0.25% in the Ashkenazi Jewish population, with a frequency of 0.12% in the total population (9/1/22 PMID: 32461654). *In silico* meta-analysis (REVEL) predicts a deleterious effect on protein function (PMID: 27666373). The c.1448T>C (p.Leu483Pro) *GBA* variant is classified as pathogenic. Clinical and biochemical correlation is required.

***GBA* c.1603C>A (p.Arg535Ser) - Uncertain Significance.** The c.1603C>A (p.Arg535Ser) missense variant results in the substitution of the arginine codon at amino acid position 535 with a serine codon. To our knowledge, this variant has not been reported in the literature as causative of disease or as a variant in the general population (9/1/22 PMID: 32461654). *In silico* meta-analysis (REVEL) is inconclusive regarding the predicted effect on protein function (PMID: 27666373). Substitutions at the same codon, p.Arg535His and p.Arg535Cys, have been reported in individuals affected with Gaucher disease (PMID: 8432537, 27735925, 32042592, 1487244, 24522292). However, there is currently insufficient evidence to determine the pathogenicity of the c.1603C>A (p.Arg535Ser) *GBA* variant, therefore this variant is classified as a variant of uncertain significance. Clinical and biochemical correlation is required.

Image 5: Gene sequencing & deletion/duplication analysis of the GBA gene s/o Gauchers disease.

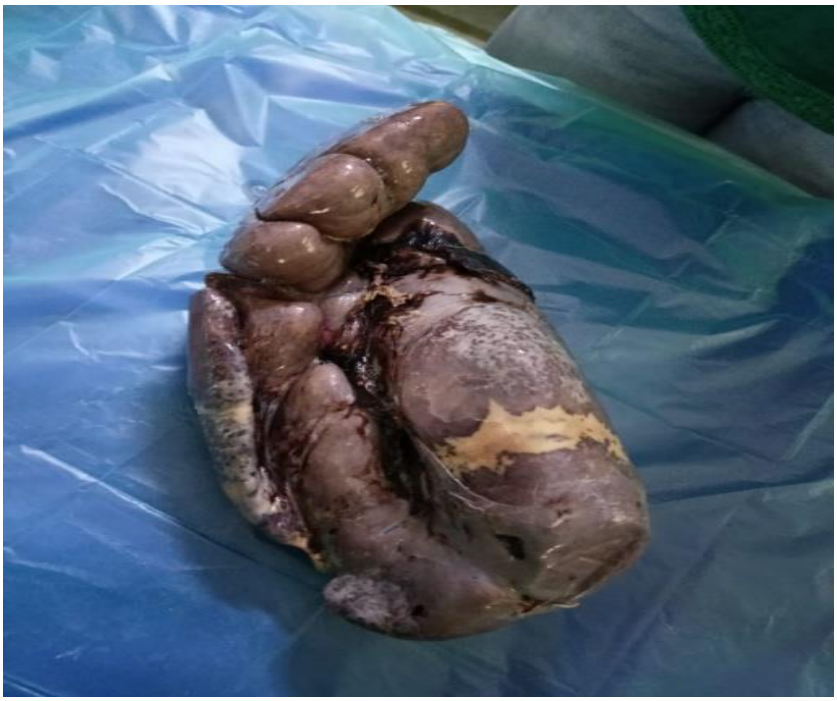

Image 6: Gross specimen of massively enlarged spleen of around 1.5 to 2 kg.

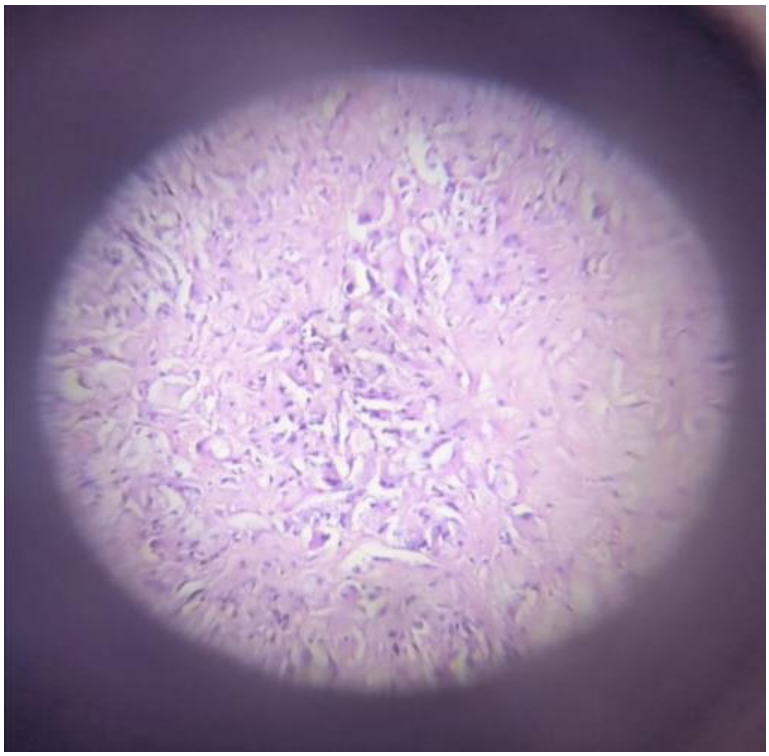

Image 7: Histology of Spleen showing multiple cells with eccentric nucleus with abundance of eosinophilic cytoplasm s/o crumpled tissue paper appearance of cytoplasm.

IV. DISCUSSION

Gauchers disease is a rare genetic disorder due to deficiency of beta- glucocerebrosidase enzyme levels which leads to deposition of beta-glucocerebroside in various organs eventually causing interference with normal functioning of cells. It has varied and multi-organ presentation.

Gold standard for diagnosis is genetic testing and enzyme levels can be used for screening. Treatment is mainly supportive. Specific treatment includes enzyme replacement therapy. Bone-marrow transplant may be beneficial only in type 3. Substrate reduction therapy might be done in few cases only.

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