GAUCHER'S DISEASE

INTRODUCTION

Gaucher's disease is the most common genetic lysosomal storage disorder caused by autosomal recessive inherited deficiency of Acid beta-glucosidase (Glucocerebrosidase). More than 400 mutations have been detected in the GBA gene located at 1q21. This results in accumulation of glycosphingolipid glucosylceramide in the lysosomes predominantly in macrophages.

NORMAL RANGE

>4 nmol/hr/mg

Beta Glucocerebrosidase In nmol/hr/mg	Remarks
>4	Normal activity
2-4	Possibility of carrier state likely
<2	Deficient activity

CLINICAL PRESENTATION

The disease phenotypes are classified as:

Type 1 (Non-neuoronopathic)

- Presence in childhood to adulthood
- Lack of neurological symptoms in 90% of cases
- Slowly to rapidly progressive visceral disease
- Distinct bimodal peaks at 10-15 years and >25 years
- Younger patients have greater hepatosplenomegaly & cytopenias
- Older patients tend to have chronic bone disease, a major cause of morbidity

Type 2 (*Acute Neuropathic*)

- Onset in infancy with brain stem dysfunction & pyramidal signs
- Rapidly progressive
- Splenomegaly common but may not be seen initially
- Bone involvement absent
- Usually fatal by 2 years of age

Type 3 (*Subacute Neuropathic*)

- Presence in early childhood
- Neurologic abnormality is usually Opthalmoplegia
- Severe presentations may show progressive Myoclonic epilepsy, Cerebellar ataxia, Spasticity & Dementia

- Mental retardation

INCIDENCE

- 1 : 1000 in Ashkenazi Jews
- 1: 40,000 – 50,000 in live births world wide

HIGH RISK FACTORS

About in 1 in 12-15 Ashkenazi Jews carry Gaucher's disease allele. 4 common mutations account for more than 85% mutations in the affected population namely N370S, 84GG, L444P & IVS2. In India L444P is the commonest mutant allele.

PATHOLOGY

- Non uniform infiltration of bone marrow by lipid laden macrophages termed as Gaucher's cells
- Infarction, ischemia, necrosis and cortical bone destruction
- Vertical compression fractures
- Aseptic necrosis of femoral head

LABORATORY DIAGNOSIS

Biochemical test

- Acid beta-glucosidase activity – 0-10% of normal

Molecular test

- Targeted mutation analysis – four common mutations tested are N370S, 84GG, L444P & IVS2. Detects:
    - 90% of disease causing alleles in Ashkenazi Jewish population
    - 50-60% of disease causing alleles in non Jewish populations.
    - Mutation N370S - most common mutation in Jews, shares a 100% association with Type 1 Gaucher's disease.
    - L444P mutation is almost always life threatening with CNS involvement.
- Sequence analysis - >150 GBA gene mutations have been described on coding entire region or exons

- Chitotriosidase - is a newly identified enzyme which is dramatically elevated in symptomatic Gaucher's patients

LIMITATIONS

- Carrier state can overlap normal state and deficient state can overlap carrier state.
- Results should be clinically correlated as individual / biological variations can affect the test results