GM2 GANGLIOSIDOSIS

(Tay-Sachs Disease & Sandhoff Disease)

INTRODUCTION

GM2 Gangliosidosis is a genetic disorder caused by deficiency of β-hexosaminidase. GM2 gangliosidosis comprises 3 different genetic and biochemical subtypes: Tay- Sachs disease, Sandhoff disease & GM2 activator deficiency (AB Variant). All three diseases have been defined together as a single disease entity GM2 gangliosidosis as they are associated with failure of the same metabolic pathway & have similar outcomes. Tay-Sachs disease corresponds to a deficiency of Hexosaminidase A, Sandhoff disease to a deficiency of Total Hexosaminidase & Hexosaminidase A enzyme. Variant AB is exceedingly rare and requires gene sequencing. It is characterized by normal Hexosaminidase A & B but the inability to form a functional GM2 activator complex.

NORMAL RANGE

Total Hexosaminidase (nmol/hr/mg)	>1150
Hexosaminidase A (%)	55

CLINICAL PRESENTATION

Infantile Form

- Tay-Sachs disease, Sandhoff disease & AB variant have a very similar presentation
- Earliest signs-motor weakness & hypotonia around 4-6 months of age
- Macular cherry red spot in retina
- Blindness, spasticity, swallowing disorder & seizures
- Macrocephaly by 18 months of age
- Doll like facies
- Child is demented & decerebrate by 3 years of age. Death often occurs due to aspiration pneumonia

Late Infantile & Juvenile Form

- Onset between 2-10 years of age
- Mostly presents as Tay-Sachs disease
- Ataxia, incoordination & dysarthria, followed by progressive psychomotor deterioration
- Spasticity
- Seizures
- Cherry red spot inconstant

Adult GM2 Gangliosidosis

- Dystonia

- Ataxia
- Psychosis in 30-50% of adult onset patients

INCIDENCE

- All types are pan ethnic.
- 1 :30 Ashkenazi jews are carriers for Tay Sachs disease

HIGH RISK FACTORS

- Genetic mutations **-** in the HEXA gene (on chromosome 15) leading to the deficiency of the enzyme hexosaminidase.
- Family history – Heterozygous parents can cause carrier state in their children. In family with an affected child, there will be 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and 25% chance of being unaffected and not a carrier.
- Consanguinity

LABORATORY DIAGNOSIS

- **Biochemical testing –** Total Hexosaminidase & Hexosaminidase A enzyme in leukocytes is deficient
- **Molecular testing -** > 130 mutations of the HEXA gene have been described worldwide. Pseudodeficiency alleles 739C-T & 745C-T reduce HEXA but do not cause illness.