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

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Hexosaminidase (nmol/hr/mg)</td>
<td>&gt;1150</td>
</tr>
<tr>
<td>Hexosaminidase A (%)</td>
<td>55</td>
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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.