# A Review on Tay-Sachs Disease

Govindarajan Sumathy[1], Bhaskaran Sathyapriya[2], Chandrakala B[*], Muhammadh Munthasir[3]

1. Professor and Head, Department of Anatomy, Sree Balaji Dental College & Hospital, Bharath Institute of Higher Education & Research, Chennai.
2. Professor, Department of Anatomy, Sree Balaji Dental College & Hospital, Bharath Institute of Higher Education & Research, Chennai.
3. Graduate student, Sree Balaji Dental College and Hospital, Bharath Institute of Higher Education and Research

*Senior Lecturer, Department of Anatomy, Sree Balaji Dental College & Hospital, Bharath Institute of Higher Education & Research, Chennai.

**Corresponding author**
Dr. Chandrakala B
Senior Lecturer,
Department of Anatomy,
Sree Balaji Dental College & Hospital,
Bharath Institute of Higher Education & Research,
Chennai

**Abstract:**

**Tay-Sachs disease (TSD) is a fatal genetic disorder that causes progressive destruction of the nervous system. It also affects the mental and physical abilities of that being around six month of age. TSD most commonly occurs in children that causes the slow destruction of the central nervous system.. It occurs when more quantities of cell membrane components called gangliosides, accumulate in the brain's nerve cells. This occurs due to the absence of an important enzyme called Hexosaminidase-A (HEX-A).**

## 1. Introduction:

Tay - Sachs disease[1,2] is an autosomal recessive disease caused by a deficiency of β-Hexosaminidase A, the lysosomal enzyme that normally degrades GM2 ganglioside. As a result, GM2 ganglioside accumulates in the lysosomes of nerve cells. Tay-Sachs disease commonly refers to the classic infantile form of GM2 ganglioside (also called type 1 GM2 gangliosidosis), wherein β-hexosaminidase A is virtually absent, juvenile and late-onset forms also occur when there is residual enzymatic activity[3,,8].

The Hex-A gene provides instructions for making a subunit of an enzyme called beta-Hexosaminidase A (Beta-Hex A) which plays a critical role in the brain and spinal cord. This enzyme is found in lysosomes (organelles that break down toxic substances). Within lysosomes, Beta-Hex A forms a part of a complex that breaks down GM2 ganglioside[4].

TSD occurs when harmful quantities of gangliosides (Component of cell membrane) accumulate in the brain's nerve cells. TSD has high incidence among Ashkenazi Jews[5], Cajuns and French Canadians. European and Russian (Ashkenazi) Jews are at high risk for developing Tay-Sachs. 1 out of every 3,600 babies born to Ashkenazi Jewish couples has the

disease. 1 in 27 are carriers in the US. rish Americans are at moderate risk, with 1 in 50 being carriers. French Canadians and the Pennsylvania Dutch are also mentionable ethnicities that are at higher risks for Tay-Sachs, whereas in the general population 1 in 250 people are carriers.

High prevalence of GM2 gangliosidosis (12 cases of Tay-Sachs disease (infantile, 9; late, 3) has been reported in children with neurological disorders from the southern region of India, consanguinity is more common [6]. Higher incidence of Tay - Sachs disease was observed in the SC community of Gujarat. The mutation p.E462V was found in six unrelated families from Gujarat indicating a founder mutation in HEXA gene[7].

**History:**

A British ophthalmologist, Warren Tay in 1881 described a patient with a cherry-red spot on the retina of the eye and a New York neurologist, Bernard Sachs gave the first description of the cellular changes in this disease. So it is named after these two physicians as Tay-Sachs disease.

**Types:**

The form is determined by the age of the individual when symptoms appear.

1. Classic Infantile Tay-Sachs symptoms appear around 6 months of age. It may be noticed in reduction in vision and the baby does not show normal startle responses.

Children gradually regress, loss of coordination, inability to swallow and difficulty breathing, losing skills one by one, unable to crawl, turn over, sit or reach out.

2. Juvenile Tay-Sachs: Symptoms typically appear between ages 2 and 5, but can occur anytime during childhood. Lack of coordination or clumsiness and muscle weakness, exhibit slurred speech, swallowing difficulties and muscle cramps, losing their ability to walk, eat on their own and communicate, prone to respiratory infections and often experience recurrent bouts of pneumonia. Many have seizures.

3. Late Onset Tay-Sachs: Symptoms typically appear in adolescence or early adulthood, but can appear later include clumsiness and muscle weakness in the legs, mental health symptoms[8].

**Symptoms:**

Begin not before 6 months of age. Child shows loss of motor skills, loss of mental functions. The child becomes blind caused by lipid-laden ganglion cells which show “cherry-red” spot on eye, deaf, paralyzed, mentally retarded and non-responsive.

**Clinical Importance:**

Affected infants lose motor skills such as turning over, sitting and crawling. They also develop an exaggerated startle reaction to loud noises. As disease progress the children with TSD experience seizures, vision and hearing loss, intellectual disability and paralysis. An eye abnormality called Cherry-Red spot can also be identified using an eye examination[9].

**Diagnosis:**

The diagnosis of Tay-Sachs disease may be confirmed by a thorough clinical evaluation and specialized tests, such as blood tests that measure the levels of hexosaminidase A in the body. Hexosaminidase A is reduced in people with Tay-Sachs disease, and absent or nearly absent in the infantile form.

Blood tests can determine whether individuals are carriers for Tay-Sachs disease. n some instances, it is possible that a diagnosis of Tay-Sachs disease may be suspected before birth (prenatally) based upon specialized tests, such as amniocentesis and chorionic villus sampling (CVS).

**Treatment:**

Treatment is directed toward the specific symptoms that are apparent in each individual. Treatment may require the coordinated efforts of a team of specialists. Paediatricians, neurologists, speech pathologists, specialists who asses and treat hearing problems (audiologists), eye specialists, and other health care professionals may need to systematically and comprehensively plan an affected child's treatment. Genetic counselling may be of benefit for affected individuals and their families. Psychosocial support is recommended for the entire family.

Research is ongoing to develop enzyme replacement therapy (ERT) for Tay-Sachs disease. Enzyme replacement therapy involves replacing a missing enzyme in individuals who are deficient or lack a particular enzyme. Synthetic versions of missing enzymes have been developed and used to treat individuals with other lysosomal storage diseases including Hurler syndrome, Fabry syndrome, and Gaucher disease. However, ERT has not proven successful in people with Tay-Sachs disease. One issue is the inability to find a way for the replacement enzyme to cross the blood-brain barrier

**Prognosis:**

Usually death of the child occurs by the age of 5. On the rare cases of Late onset of TSD, the children's death occurs as soon as they reach their Teens. Hence provision of symptomatic care ensures the easy living of the children diagnosed with TSD.

## 2. Conclusions:

TSD is an autosomal recessive neurodegenerative disorder caused by the deficiency of the lysosomal enzyme β-hexosaminidase A (HexA), which result in the accumulation of GM2 gangliosides mainly in neurons[3]. There is no effective treatment approved to treat TSD. though, various methods have been investigated to restore the function of β-hexosaminidase A. Gene therapies to restore enzymes in patients could offer treatment for these diseases but more studies and research are needed as they currently have multiple limitations. Concentration to the importance of conducting research on this disease in order to provide timely treatment and achieve good prognosis for patients is considered necessary[10].

TSD is an autosomal recessive neurodegenerative disorder caused by the de□ciency of the lysosomal enzyme β-hexosaminidase A (HexA), which result in the accumulation of GM2 gangliosides mainly in neurons. It has an estimated prevalence of 1 per 220 000 individuals and patients usually die before 5 years of age.

There is no effective treatment approved to treat TSD nor to stop its progression; however, various methods have been explored to restore the function of β-hexosaminidase A. Gene therapies to restore enzymes in patients could offer treatment for these diseases but more studies and research are needed as they currently have multiple

limitations. Gathering existing information on the pathology allows emphasizing the importance of conducting research on this disease in order to provide timely treatment and achieve good prognosis for patients.

**3. Bibliography:**

**1.** Tay-Sachs Disease by: Robert J. Desnick and Michael Kaback
**2.** Tay-Sachs Disease by: Julie Walker
**3.** Kaback MM, Desnick RJ. Hexosaminidase A Deficiency. 1999 Mar 11 [updated 2011 Aug 11]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, Seattle (WA): University of Washington, Seattle.
**4.** Hall P, Minnich S, Teigen C, Raymond K. Diagnosing lysosomal storage disorders: the GM2 gangliosidosis. Curr Protoc Hum Genet. 2014
**5.** Steiner KM, Brenck J, Goericke S, Timmann D. Cerebellar atrophy and muscle weakness: late-onset Tay-Sachs disease outside Jewish populations. BMJ Case Rep. 2016.
6. Nalini A, Christopher R. Cerebral glycolipidoses: clinical characteristics of 41 pediatric patients. J Child Neurol. 2004;19(6):447– 452..
7. 10. Mistri M, Tamhankar P, Sheth F, et al. Identification of novel mutations in HEXA gene in children affected with Tay Sachs disease from India. PLoS One. 2012;7(6):e39122. doi: 10.1371/journal.pone.0039122.
**8.** Neudorfer O, Pastores GM, Zeng BJ, Gianutsos J, Zaroff CM, Kolodny EH. Late-onset Tay-Sachs disease: phenotypic characterization and genotypic correlations in 21 affected patients
**9.** Molecular pathophysiology in Tay–Sachs and Sandhoff diseases as revealed by gene expression profiling ; Rachel Myerowitz, Douglas Lawson, Hiroki Mizukami, Yide Mi, Cynthia J. Tifft, Richard L. Proia
10. Utz JR, Crutcher T, Schneider J, Sorgen P, Whitley CB. Biomarkers
11. of central nervous system inflammation in infantile and juvenile ganglio-
12. sidoses. Mol Genet Metab. 2015;114(2):274-80. http://doi.org/f6z3xz.
13. 19. Kitakaze K, Mizutani Y, Sugiyama E, Tasaki C, Tsuji D, Maita
14. N, et al. Protease-resistant modified human β-hexosaminidase B
15. ameliorates symptoms in GM2 gangliosidosis model. J Clin Invest.
16.
17. 2016;126(5):1691-703. http://doi.org/c2vd.
18. 20. Sinici I, Yonekawa S, Tkachyova I, Gray SJ, Samulski RJ, Wakar-
19. chuk W, et al. In cellulo examination of a beta-alpha hybrid construct of
20. beta-hexosaminidase A subunits, reported to interact with the GM2 activa-
21. tor protein and hydrolyze GM2 ganglioside. PloS One. 2013;8(3):e57908.
22. http://doi.org/f4qbp
23. Utz JR, Crutcher T, Schneider J, Sorgen P, Whitley CB. Biomarkers
24. of central nervous system inflammation in infantile and juvenile ganglio-
25. sidoses. Mol Genet Metab. 2015;114(2):274-80. http://doi.org/f6z3xz.
26. 19. Kitakaze K, Mizutani Y, Sugiyama E, Tasaki C, Tsuji D, Maita
27. N, et al. Protease-resistant modified human β-hexosaminidase B
28. ameliorates symptoms in GM2 gangliosidosis model. J Clin Invest.
29.
30. 2016;126(5):1691-703. http://doi.org/c2vd.
31. 20. Sinici I, Yonekawa S, Tkachyova I, Gray SJ, Samulski RJ, Wakar-
32. chuk W, et al. In cellulo examination of a beta-alpha hybrid construct of

33. beta-hexosaminidase A subunits, reported to interact with the GM2 activa-
34. tor protein and hydrolyze GM2 ganglioside. PloS One. 2013;8(3):e57908.
35. http://doi.org/f4qbp
10. Ferreira CR, Gahl WA. Lysosomal storage diseases. Transl Sci Rare Dis. 2017;2(1-2):1-71. http://doi.org/gckhg7
Utz JR, Crutcher T, Schneider J, Sorgen P, Whitley CB. Biomarkers of central nervous system inflammation in infantile and juvenile gangliosidoses. Mol Genet Metab. 2015;114(2):274-80. http://doi.org/f6z3xz.
19. Kitakaze K, Mizutani Y, Sugiyama E, Tasaki C, Tsuji D, Maita N, et al. Protease-resistant modified human β-hexosaminidase B ameliorates symptoms in GM2 gangliosidosis model. J Clin Invest.

2016;126(5):1691-703. http://doi.org/c2vd.
20. Sinici I, Yonekawa S, Tkachyova I, Gray SJ, Samulski RJ, Wakarchuk W, et al. In cellulo examination of a beta-alpha hybrid construct of beta-hexosaminidase A subunits, reported to interact with the GM2 activator protein and hydrolyze GM2 ganglioside. PloS One. 2013;8(3):e57908. http://doi.org/f4qbp
Utz JR, Crutcher T, Schneider J, Sorgen P, Whitley CB. Biomarkers of central nervous system inflammation in infantile and juvenile gangliosidoses. Mol Genet Metab. 2015;114(2):274-80. http://doi.org/f6z3xz.
19. Kitakaze K, Mizutani Y, Sugiyama E, Tasaki C, Tsuji D, Maita N, et al. Protease-resistant modified human β-hexosaminidase B ameliorates symptoms in GM2 gangliosidosis model. J Clin Invest.

2016;126(5):1691-703. http://doi.org/c2vd.
20. Sinici I, Yonekawa S, Tkachyova I, Gray SJ, Samulski RJ, Wakarchuk W, et al. In cellulo examination of a beta-alpha hybrid construct of beta-hexosaminidase A subunits, reported to interact with the GM2 activator protein and hydrolyze GM2 ganglioside. PloS One. 2013;8(3):e57908. http://doi.org/f4qbp