Tay-Sachs Disease: A Deadly Inherited Disorder

Muhammad Faseeh Ullah Khan

1st Year MBBS, Islamabad Medical and Dental College, Islamabad, Pakistan

Key points:

- Introduction
- Causes
- Symptoms
- Diagnosis
- Treatment
- Conclusion

Introduction

Tay-Sachs disease is an inherited, life threatening condition where nerve cells in the brain and spinal cord degenerate and die. This leads to progressive neurological dysfunction. A deficiency in the enzyme that breaks down a fatty substance in nerve cells, Hex-A, may cause Tay- Sachs disease. This deficiency stems from inheriting a mutated form of the gene — coding for the specific enzyme— that a person inherits from each parent. Symptoms of the condition can vary, depending on the form of the condition the person acquires, but they may include muscle weakness and difficulties swallowing. Currently, there is no cure for Tay- Sachs. Treatment involves supportive measures, such as providing adequate nutrition, maintaining hygiene, preventing infections, and providing musculoskeletal support. Even with optimal care, the typical life expectancy for individuals with the infantile form is 4 to 5 years.[1]

Tay-Sachs disease involves progressive neurological degeneration. There are three forms of the condition:

- Classic infantile: This is the most common form and can appear in infants around 6 months old.

- Juvenile: This form typically manifests in children aged 2 to 5 years, but it can occur any time during childhood.

- Late-onset: This form typically occurs in adolescence or young adulthood, although some cases may appear later.

Tay- Sachs diseases is also goes by a few other names, such as:

- B variant GM2 gangliosidosis
- Hex- A deficiency
- GM2 gangliosidosis type 1
- hexos aminidase A deficiency
- sphingolipidosis
- hexos aminidase alpha-subunit deficiency (variant-B)

As an estimated 5,000 individuals in the United States have Tay-Sachs Disease, according to the National Center for Advancing Translational Sciences.[2]

In the general population, per the National Library of Medicine (NLM), it affects approximately 1 in 1,000,000 live births, and the carrier frequency is 1 in 250.[3]
(A carrier is a person who does not have the condition but can pass it on to their children)

Groups with a higher prevalence include:

- Ashkenazi Jewish heritage, which denotes the Jewish population of Central or Eastern European ancestry
- The Old Order Amish community in Pennsylvania
- Cajun community in Louisiana
- Non-Jewish French Canadians who live near the St.Lawrence River

Causes

A deficiency of the enzyme beta-hexosaminidase (Hex-A) causes Tay-Sachs disease. GM2 ganglioside is a fatty substance that is part of the body's normal functioning, but it needs to be broken down. The body uses Hex-A to break it down. When insufficient Hex-A is available, GM2 ganglioside builds up atypically in cells in the brain and spinal cord. This leads to cell degeneration and death. Triggering an immune response, these effects may cause damage to surrounding tissue as well as progressive damage to these structures over time.[4]

The condition stems from a gene mutation on chromosome 15 that codes for Hex-A production. Every person has two copies of this gene, one from each parent. If at least one copy of the gene is normal, their body makes enough Hex-A. People with one normal and another abnormal, or mutated, gene are health, but they are carriers.[5]

People inherit this condition in an autosomal recessive pattern.

When both parents are carriers — and their child inherits the mutated gene from them both—the child will have Tay-Sachs. If both parents are carriers, each child has a 25% likelihood of having the condition and a 50% risk of being a carrier, according to the NLM.

Symptoms

Below are the symptoms of the different forms of Tay- Sachs:

Infantile Tay- Sachs Disease:

A baby develops normally in the first 6 months. Afterward, their development slows, and parents may notice changes in the child's development. Over time, an infant loses developmental skills they acquired, such as crawling and turning over. They also progressively have difficulty breathing and lose their ability to swallow.[6]

At age 2, most children may experience recurrent seizures, as well as a loss of vision, mental skill, and muscle function.

Juvenile Tay- Sachs Disease:

Early symptoms may include muscle weakness, clumsiness and lack of coordination. Over time, however, children may lose the ability to eat on their own, communicate and even their ability to walk.
Additionally, they tend to have recurrent infections, and many experience seizures.

Late-on set Tay- Sachs Disease:

Early symptoms include muscle weakness in the legs, and clumsiness. After diagnosis, people may reflect back to their childhood and remember that they had signs, such as stuttering or a lack of athletic ability. Approximately 40% have mental health symptoms, such as psychosis or bipolar episodes.[7]

Over time, such individuals experience a slow-progressive decline in mobility along with swallowing and speech difficulties.

Diagnosis

The diagnostic process may require:

- History and physical examination: Doctors may note down neurological symptoms the infant is experiencing and look for signs of the condition.
- Hex-A blood tests: People with the infantile form will have no or extremely low levels of Hex-A, while those with the juvenile or late-on set form may retain levels of 10–15%.4,5,8
- MRI scans: MRI scans and similar tests may provide images of the brain to assess for damage.
- Molecular testing: To check for mutations in the gene that codes for Hex- A can confirm a diagnosis. According to the National Human Genome Research, this procedure detects about 60% of carriers in the general population and about 95% of carriers with an Ashkenazi Jewish background.

Treatment

Currently, there is no cure for Tay- Sachs disease. However, there are ways to manage the disease, such as:[9]

- managing seizures
- providing adequate nutrition
- protecting the airway for breathing
- managing infections
- offering early comprehensive occupational and physical therapy.[9]

Conclusion

To summarize, Tay-Sachs involves progressive neuro degeneration — even with optimal care — individuals with the infantile form typically have a life expectancy of 4 to 5 years. Death is normally due to recurrent infections.

People with the late- on set form frequently require mobility assistance, and their psychiatric symptoms often do not respond well to treatment. Progression of the condition often leads to a vegetative state and may lead to death in children aged10 to 15years.

While it is rare in the general population, it occurs more frequently in certain people groups, such as those of Ashkenazi Jewish heritage.

The condition results from a deficiency in Hex-A, an enzyme that prevents the accumulation of a fatty substance in the nerve cells. This happens when someone inherits a pair of mutated genes that code for the body's Hex- A synthesis.

Symptoms vary with the form of Tay- Sachs, but they all involve a loss of mental or motor function. Typically, doctors diagnose this condition with an array of tests. A molecular genetic test may be helpful in certain populations—people may want to consult with a genetic counselor to discuss what this test, and its results may indicate.[10]

Currently, there is no cure for the disease, so treatment focuses on providing support and increasing a person's quality of life.

References

1. Gravel RA, Kaback MM, Proia RL, et al. The GM2 gangliosidoses. In: Valle DL, Antonarakis S, Ballabio A, et al., editors. The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill; 2019.
2. National Center for Advancing Translational Sciences (NCATS). Tay-Sachs disease. Genetic and Rare Diseases Information Center; 2023. [https://rarediseases.info.nih.gov/diseases/7737/t ay-sachs-disease]
3. Kaback MM. Population-based genetic screening for reproductive counseling: the TaySachs disease model. Eur J Pediatr. 2000.
4. Mahuran DJ. Biochemical consequences of mutations causing the GM2 gangliosidoses. Biochem Biophys Acta. 1999.
5. Myerowitz R. Tay-Sachs disease-causing mutations and neutral polymorphisms in the Hex A gene. Hum Mutat. 1997.
6. Kolodny EH, Raghavan S, Krivit W. Lateonset Tay-Sachs disease: natural history and treatment with OGT 918 (Zavesca). J Neurochem. 2004.
7. Shapiro BE, Hatters-Friedman S, FernandesFilho JA, et al. Late-onset Tay-Sachs disease: adverse effects of medications and implications for treatment. Neurology. 2006.
8. Triggs-Raine BL, Mules EH, Kaback MM, et al. A pseudodeficiency allele common in nonJewish Tay-Sachs carriers: implications for carrier screening. Am J Hum Genet. 1992.
9. Platt FM, d'Azzo A, Davidson BL, et al. Lysosomal storage diseases. Nat Rev Dis Primers. 2018.
10. Delgado MR, Proud VK. Genetic counseling in Tay-Sachs disease. J Genet Couns. 2008.