

Disease statistics

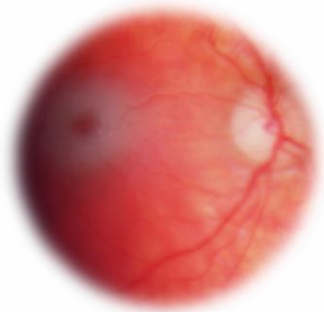
TAY-SACHS DISEASE- AUTOSOMAL RECESSIVE GENETIC DISORDER

TAY-SACHS DISEASE

- Tay-Sachs Disease 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.
- The disease is one of the family of lysosomal storage disorders known as GM2 gangliosides, each determined by the specific peptide (α and β subunits of β -hexosaminidase A and the GM2 activator protein) that is defective in the degradation of GM2 ganglioside.
- It is a rare fatal genetic disorder in children that causes the slow destruction of the central nervous system.

HISTORY

- The disease is named after Warren Tay (1843-1927), a British ophthalmologist who in 1881 described a patient with a cherry-red spot on the retina of the eye.
- It is also named after Bernard Sachs (1858-1944), a New York neurologist whose work several years later provided the first description of the cellular changes in Tay-Sachs Disease.
- Sachs also recognized the familial nature of the disorder, and, by observing numerous cases, he noted that most babies with Tay-Sachs Disease at that time were of Eastern European Jewish origin.
- Today, Tay-Sachs is found to occur among people of all backgrounds.



Cherry red spot in the eye is the sign of Tay -Sachs disease

WHO IS AT RISK?

- European and Russian (Ashkenazi) Jews are at high risk for developing Tay-Sachs. 1 in 27 in the US are carriers.
- 1 out of every 3,600 babies born to Ashkenazi Jewish couples have the disease.
- 1 in 27 are carriers in the US.
- Irish 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 G[M2-M3] gangliosidosis, 3) has been reported in children with neurological disorders from the southern region of India, consanguinity is more common [7].
- 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 [5].

TYPES OF TAY-SACHS DISEASE

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

Only one form of Tay-Sachs occurs in a family. If a child has Infantile, older siblings are not at risk to develop Juvenile or Late Onset Tay-Sachs later in life.

I. Classic Infantile Tay-Sachs: Symptoms appear around 6 months of age. Parents may notice a reduction in vision and tracking and the baby does not outgrow normal startle response.

- Infantile Tay-Sachs children gradually regress, losing skills one by one. Over time they are unable to crawl, turn over, sit or reach out. Other symptoms include loss of coordination, progressive inability to swallow and difficulty breathing.
- By age 2 and beyond, most children experience recurrent seizures and eventually lose muscle function, mental function and sight, becoming mostly non-responsive to their environment.

TYPES OF TAY-SACHS DISEASE

2. Juvenile Tay-Sachs: Symptoms typically appear between ages 2 and 5, but can occur anytime during childhood.

- Early symptoms of Juvenile Tay-Sachs include lack of coordination or clumsiness and muscle weakness such as struggling with stairs. A child may also exhibit slurred speech, swallowing difficulties and muscle cramps.
- Over time, children with Juvenile Tay-Sachs slowly decline, losing their ability to walk, eat on their own and communicate. Children are prone to respiratory infections and often experience recurrent bouts of pneumonia. Many have seizures.
- Juvenile Tay-Sachs has a broad range of severity. In most cases, the earlier the first signs are observed, the more quickly the disease will progress.

TYPES OF TAY-SACHS DISEASE

3. Late Onset Tay-Sachs: Symptoms typically appear in adolescence or early adulthood, but can appear later.

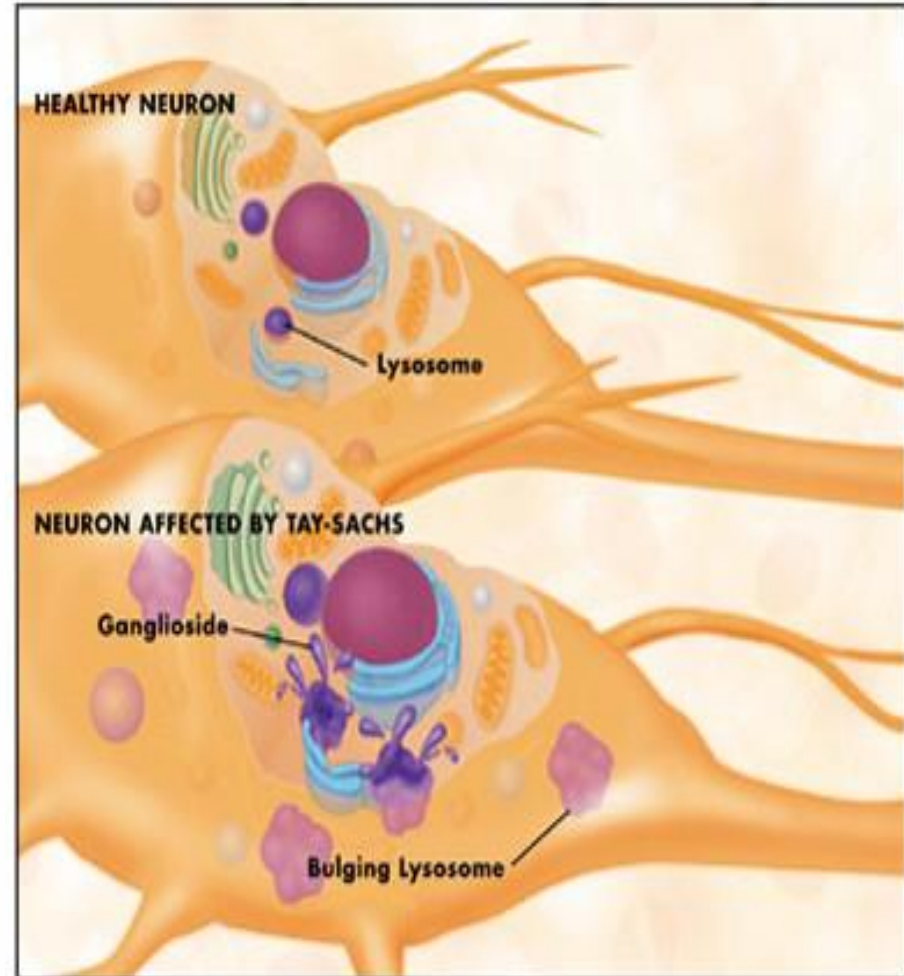
- Early symptoms of Late Onset Tay-Sachs (LOTS) include clumsiness and muscle weakness in the legs. Once diagnosed, adults often reflect back to their childhood and may notice experiencing symptoms much earlier such as not being athletic and/or speech difficulties or a stutter as a child or teenager.
- The mental health symptoms may present first which can lead to an especially long road to diagnosis. About 40% of affected adults experience mental health symptoms such as bi-polar or psychotic episodes.
- Gradual Loss of skills - Over time adults with Late Onset Tay-Sachs slowly decline. Adults frequently require more mobility assistance, i.e. cane to walker to wheelchair. Many experience speech and swallowing difficulties but few require a feeding tube.

CAUSES

Tay-Sachs Disease is caused by the absence or significantly reduced level of a vital enzyme called beta-Hexosaminidase.

It is the Hexosaminidase A (Hex-A) gene in the DNA that provides instructions for making this enzyme.

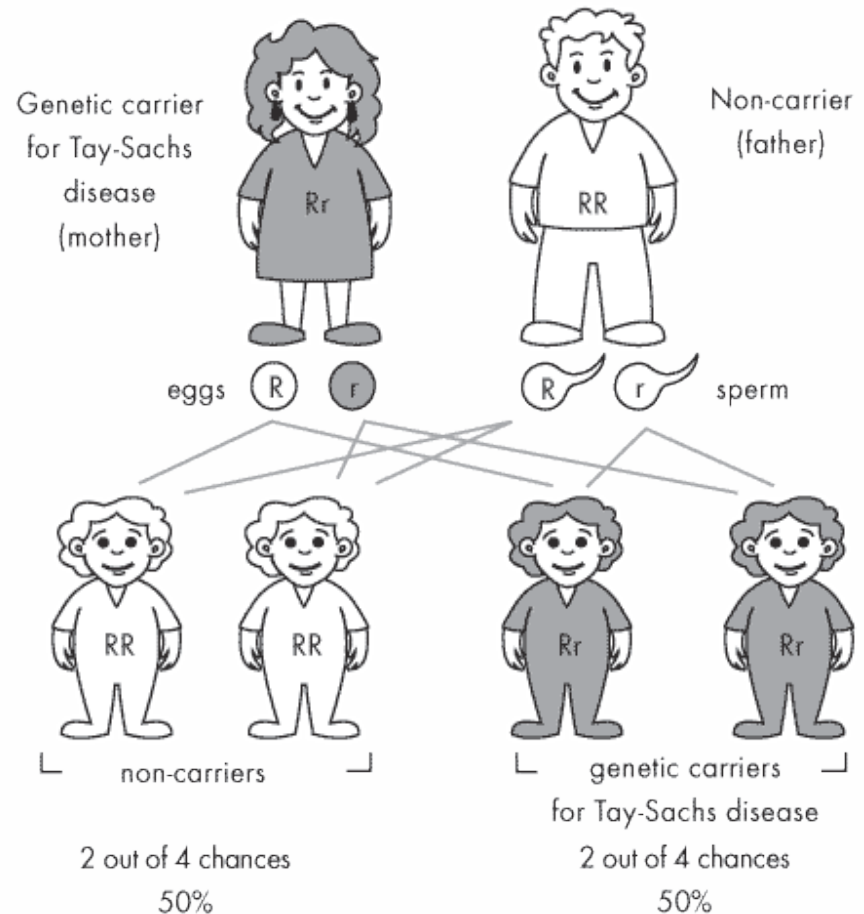
Without the correct amount of the Hex-A enzyme, a lipid called GM2 ganglioside accumulates abnormally in cells, especially in the nerve cells of the brain causing progressive damage to the cells. Infantile Tay-Sachs is typically the absence of the Hex-A enzyme. This differs from the Juvenile and Late Onset forms of Tay-Sachs when the mutations allow the Hex A enzyme to function a little bit. Just a small increase in Hex A activity is enough to delay the onset and slow the progression of symptoms.



INHERITANCE

Tay-Sachs is an autosomal recessive genetic disorder. If both parents are carriers, there is a 25% chance with each pregnancy that the child will be affected. Carriers of recessive diseases do not experience any adverse health effects.

Tay-Sachs "breeds true" in a family. If one child is diagnosed with Infantile Tay-Sachs, the other children are only at risk for the infantile form. The gene that causes Tay-Sachs is located on chromosome 15, specifically 15q23-q24.



DIAGNOSIS

Enzyme assay

- Measuring activity of both Hex A and Hex B in serum/leukocytes by fluorimetric study [8]
- Decreased activity of Hex A with normal or increased activity of Hex B in carriers [3]

DNA analysis- When enzymatic assays show Hex-A deficiency, DNA analysis is essential to confirm the phenotype and evaluate the possible progression of the disease regarding the genotype. DNA analysis is also useful for population screening, as carried out on Jewish, in order to identify carriers and couples at risk of breeding affected children and receive proper genetic counselling.

Prenatal diagnoses can be performed with amniotic fluid or chorionic villus samples [2] [1].

Pre-conceptual counselling for at risk couples- Screening for the Hex-A mutation that causes Tay-Sachs Disease is recommended if you are planning to start a family and you are in a high-risk group for developing the disease.

DIAGNOSIS

Genetic tests- Although there is a 75% chance of having a healthy baby naturally if you and your partner are carriers of Tay-Sachs disease, it is possible to avoid any risk of having a child with the condition through *in-vitro* fertilization (IVF). The resulting embryos can be tested and only healthy embryos are selected for implantation in the womb.

Electromyogram

Denervation and re-innervation may be seen in the adult chronic form.

CT Scan of brain

Area of low density in basal ganglia and cerebral white matter.

MRI Brain

Increased signal in basal ganglia and cerebral white matter.

MANAGEMENT

THERE IS NO EFFECTIVE TREATMENT FOR TAY-SACHS DISEASE. ENZYME REPLACEMENT HAS NOT YET BEEN SUCCESSFUL.

Treatment usually focuses on:-

Treatments	Reason for treatment
Medication	To manage pain or seizures in TSD patients.
Respiratory care	To solve the difficulties with breathing. Example: Chest physiotherapy is used to reduce mucus.
Feeding tubes	To solve swallowing problem. Example: Nasogastric (NG) tube helps to deliver nutrients through the nose and esophagus into the stomach. Percutaneous esophago-gastrostomy (PEG) tubes inserted surgically.
Physical therapy	To prevent deterioration of neurological and motor functions in TSD patients.

TAY-SACHS RESEARCH

To date, there is no treatment or cure for Tay-Sachs Disease but research is making exciting advances towards a treatment and a cure.

Ongoing research is being conducted to use new technology and advances in biomedical research to find a treatment.

1. Substrate Deprivation-

- The goal of substrate deprivation therapy is to decrease the amount of gangliosides GM2 produced by the cells.
- This treatment only helps to prevent future build-up of gangliosides and does not repair any accumulation that has already occurred. This is a problem because in classical and juvenile Tay-Sachs, buildup of gangliosides begins early in development. By the time the child is born and exhibiting symptoms to warrant the treatment, the treatment would not be effective.

2. Enzyme replacement Therapy-

- Several ERT techniques have been investigated for lysosomal storage disorders, and could potentially be used to treat Tay-Sachs Disease.
- The goal would be to replace the missing enzyme, a process similar to insulin injections for diabetes.
- However, the Hex-A enzyme has proven to be too large to pass through the blood into the brain through the blood-brain barrier.
- Researchers have also tried instilling the enzyme into cerebrospinal fluid, which bathes the brain. However, neurons are unable to take up the large enzyme efficiently even when it is placed next to the cell, so the treatment is still ineffective.

3. Chemical Chaperones-

- Chemical chaperones are small inhibitors that would help stabilize the abnormal Hex-A enzyme and allow it to be transported to the lysosome where it could help break down some of the accumulated gangliosides.
- This approach has the potential to help both classical and late onset forms of Tay-Sachs.

4. Bone marrow transplantation-

- It is reportedly effective in preventing the progression of neurological deterioration in lysosomal storage disorders.
- Recent research on stem cell biology suggests that bone marrow cells contain non-hematopoietic stem cells, including brain precursor cells.
- Bone marrow contains cells capable of differentiating into oligodendrocytes, astrocytes, and microglia when exposed to the brain microenvironment. Autologous bone marrow cells may be useful as carriers for ex vivo gene therapy for lysosomal disorders with neurological symptoms [6].

5.Stem Cells-

- Currently, animal models for Tay-Sachs are being developed to explore transplanting **neural stem cells** into the central nervous system.

It is known that human neural stem cells have the ability to differentiate into different neural cell types. In addition, human neural stem cells can migrate throughout the mice brain after an intra-cerebral injection.

Exciting breakthrough work on the potential therapeutic uses of stem cells was done in Sandhoff mice. Stem cell therapy is still an emerging field; potential therapies or clinical trials using stem cell therapy is not immediate.

- Another form of stem cell research being explored is **mesenchymal bone marrow cells**.

It would be easier to use these types of stem cells because they are more easily obtained than neural stem cells. They can be derived or transferred from the individual's body that is in need of the treatment. This reduces the chance of rejection.

Also, mesenchymal bone marrow cells have the ability to differentiate and migrate throughout the brain after an intra-cerebral injection just as neural stem cells can.

- Another source of stem cells is **Umbilical cord blood**. **Martin, Carter, Kernan, Sahdev, Wall, Pietryga et al. (2006)** investigated the use of stem cells in cord blood to treat lysosomal and peroxisomal storage diseases (LSDs) in 69 children (mean age = 1.8 years), 3 of which had Tay-Sachs Disease.

Survival improved with higher matches of antigens of the cord blood cells to the patient.

Results suggest that stem cell transplantation is a viable method of prolonging life in Lysosomal storage diseases patients [4].

TAY-SACHS CHILDREN RESPOND TO GROUND BREAKING STEM CELL GENE THERAPY

- Dr. Feinerman developed methods to increase enzyme activity, empty substrates that formed in cells, and correct non-functioning misfolded proteins.

In November 2010, Dr. Feinerman and Dr. Paino administered treatment to Aspen Brown, a 14-month-old child from Alabama suffering from Tay-Sachs. Aspen was the first child to receive the treatment. Within days of the treatment she exhibited improvement in muscle tone, the ability to move her head and neck, follow movement, and grasp objects.

In April 2011, Dr. Feinerman and Dr. Paino took their research one step further by inserting the Hex-A gene into neuron stem cells without using a viral vector.

The gene treatment was provided to three children at the Concebir Clinic in Lima, Peru. Although Dr. Feinerman and Dr. Paino were not expecting any miracles from the treatment, they were greeted by the overjoyed parents of the children at the hospital just two days later.

The children were making sounds, showing active facial expressions, moving their arms and legs, following moving objects, making head and neck movements, showing increased muscle tone, swallowing more and exhibiting a decrease in drooling.

Two of the children had been suffering from multiple seizures a day, but those seizures stopped shortly after the treatment.

CASE STUDIES ON STEM CELL BASED THERAPY FOR TAY-SACHS DISEASE

- The most successful is the Umbilical cord blood transplant done in a child named Jordan Lehman - he was transplanted at 14 months and at age 8 is actually gaining skills.
- Hunter Combs is now eight years old after being transplanted at 14 months.
- Krystie Karl-Steiger was transplanted in May 2007 at the University of Minnesota - she continues to recover.

Cord blood transplants to treat genetic metabolic disorders in babies while they are still in the womb is a method which uses a small select number of therapeutic stem cells injected directly into the foetus's abdomen at 12-14 weeks pregnancy.

The idea is to give the baby cord blood stem cells from a healthy donor with the potential to provide healthy genes that will hopefully replace the genes that aren't working in the baby's cells.

There is a pilot trial currently open to pregnant women at risk for having children with fatal metabolic disorders including Tay-Sachs Diseases.

The trial is being conducted out of Duke University Medical Center in Durham, N.C.

The Cord Blood Transplantation Study (COBLT), sponsored by the National Heart, Lung, and Blood Institute, patients with Tay-Sachs Disease (n = 3).

One-year survival was 72% (95% confidence interval, 61%-83%). The cumulative incidence of neutrophil engraftment by day 42 was 78% (95% confidence interval, 67%-87%) at a median of 25 days.

Cord blood transplantation should be considered as frontline therapy for young patients with lysosomal and peroxisomal storage diseases [4].

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Thank you

