Tay-Sachs Disease
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Tay-Sachs Disease is an autosomal recessive neurodegenerative disorder that is typically fatal within the first two or three years of life. Its incidence is highest among Ashkenazi Jews (Jews of Eastern European descent), approximately 100 times higher than in the general population. Juvenile and adult onset variants of the disease exist, but are extremely rare and will not be discussed here. The disease was characterized by two doctors working independently, resulting in its hyphenated name; a British physician named Warren Tay, and an American physician named Bernard Sachs. Tay, an ophthalmologist was, in 1881, the first to notice the characteristic red spot on the eye that is now considered a typical finding in the disease. Sachs, researching independently from Tay, began to characterize this syndrome, noting its familial characteristics and propensity to appear in Jewish children. In addition to the ophthalmologic findings made by Tay, Sachs, in 1887, characterized the disease as involving a halt to mental development, a deficiency in normal reflexes, progressive blindness, paresis, and mortality at about two years of age.¹

Symptomology
A thorough understanding of the symptoms of the disease is essential for the physician in order to arrive at a correct diagnosis. Symptoms typically found include retardation beginning early in infancy followed by dementia, blindness, and paralysis. Infantile Tay-Sachs usually proves to be fatal by the age of three.²

A study done by Rapin et al. in 1976, assessed the condition of a brother and two sisters of Ashkenazi descent who were diagnosed with Tay-Sachs. Early in childhood, the children lost their ability to walk and maintain posture. Furthermore they showed loss of muscle mass, foot drop, muscle spasms, as well as loss of coordination in their trunk and extremities. Although the muscle atrophy began in the lower limbs, it soon reached the upper body, causing stuttering due to the denervation of laryngeal muscles. Furthermore, a characteristic "cherry-red" spot in the back of their retina was discovered as a consequence of the neural degeneration in the CNS. Although displaying many of the signs of classical Tay-Sachs, these children did not display the usual loss of optic acuity and intelligence. After one of the children died, biochemical studies showed that this family did indeed have an allelic variant of the disease.²

Diagnosis, Testing, and Prevention
Tay-Sachs is most prevalent in the Ashkenazi Jewish population with a carrier rate of 1 in 25, as opposed to the rate of 1 in 250 in the general population. This high carrier rate has caused the Jewish population, in both Israel and around the world, to place more emphasis on genetic screening and testing. In fact, Tay-Sachs screening in the Jewish community is one of the first successes for genetic screening for a specific genetic disorder. Carrier detection and prevention programs have proven dramatically effective and have established the paradigm for the prevention of recessive diseases. “Since 1970, more than 1.4 million individuals worldwide have been screened voluntarily to determine if they are carriers of the mutant gene for Tay Sachs Disease.” In the United States alone, the incidence of Tay Sachs in the Jewish population has decreased by more than ninety
percent. The diagram below clearly shows the dramatic difference genetic testing has had in eliminating this disease.

![Impact of Carrier Testing for Tay-Sachs Disease](image)

Individuals carrying Tay Sachs mutations show a reduced level of the enzyme Hexosaminidase A which is essential for breaking down fatty substances in neural tissue. As a result these lipid molecules build up in the CNS and gradually destroy neural structures. A routine and inexpensive carrier test is a blood test measuring the level of hexosaminidase activity.

Besides enzyme assays of hexosaminidase A activity, diagnosis can also be done via genetic testing using polymerase chain reaction. The latter method is used when the ancestry of both parents is known. This allows for the detection of specific genetic markers. Although it is more specific, it is also much more expensive. Prenatal diagnosis is done when both parents are known to be carriers to assess whether the fetus is homozygous for the mutant alleles. This then allows the parents to decide whether they want to terminate the pregnancy should the fetus test positive.

Besides enzyme assay activity and genetic screening, eye exams can also help in the diagnosis of Tay Sachs. As mentioned above, affected individuals have a characteristic “cherry red” spot in the eye due to the displacement of the optic nerve into the orbit. In 1968, a study by Balint, et al., showed that homozygous affected and heterozygous individuals had reduced levels of the lipid sphingomyelin, in their red blood cells. Therefore measuring levels of this lipid in the blood gives us yet another biochemical tool for detecting carriers.

In some orthodox Ashkenazi Jews, a special screening program called Dor Yeshorim screens individuals for the common Tay-Sachs mutant alleles to determine if there is any risk they could have a child with Tay-Sachs. A marriage between two carriers would result in a 25% chance that their child would be affected with Tay-Sachs. Because
of this, Dor Yeshorim strongly recommends against marriage between individuals who are both carriers.\textsuperscript{8}

**Disease Risks for Other Family Members**

As mentioned above, Tay-Sachs is inherited in an autosomal recessive pattern. Only homozygotes for the mutant allele display the phenotype of Tay-Sachs. For a Tay-Sachs child to be born, both parents have to be carriers of the mutant allele. If this is the case, there is a 25\% chance that this couple will have an affected child. However, two thirds of the healthy children from these parents will still be heterozygous i.e. carriers for the mutant allele. When a couple has a Tay-Sachs child, this indicates the presence of mutant allele their family’s gene pool. This knowledge has a great effect on many members of the family. The parents must be made aware that for each child there is a new 25\% chance that the baby will have the disease. Furthermore, if each parent is a carrier that means that this mutant allele can be found in one of their parents. So one of the maternal grandparents and one of the paternal grandparents are carriers for the mutant allele. Once we know that one grandparent from each set is a carrier we can then turn our attention to all the aunts and uncles. Each aunt and uncle has a 50\% chance of being a carrier as they have a 50\% chance of inheriting the mutant allele from their heterozygous parent. This can affect their children if their mate is also a carrier. This knowledge can prove crucial in family planning.

**Biochemistry and Genetics**

Tay-Sachs is classified as a lysosomal storage disease. The normal function of the affected protein, $\beta$-hexosaminidase A, is to degrade a compound called GM2-ganglioside, a fatty-acid derivative. Without this degradation, GM2-ganglioside builds up in the lysosomes of neuronal tissue, leading to the neurodegenerative effects of the disease. While massive neuronal apoptosis is observed in patients with Tay-Sachs, the exact method through which the GM2-gangliosides cause this has yet to be determined. Gene expression profiles in diseased individuals demonstrate the presence of an intense inflammatory process. It is hypothesized that astrocytes and microglia become activated in response to the initial neuronal damage to release inflammatory cytokines which trigger the apoptosis present in this disorder.\textsuperscript{9}

In the form of Tay-Sachs found in Ashkenazi Jews, the major defect is an insertion in the $\alpha$-chain of the gene for $\beta$-hexosaminidase A, also known as HEXA. The disease is inherited in an autosomal recessive manner with the carriers displaying no visible disease phenotype. As an autosomal recessive disease, the risk for two carrier parents to have an affected child is one in four. Thanks to rigorous testing among the Ashkenazi population, the number of affected children born to Ashkenazi families has actually dropped below the number of affected children born to non-Ashkenazi families. The high incidence of the mutation in the Ashkenazi Jewish population would seem to indicate a founder effect, and in fact a single mutation appears to account for 70\% of the carriers in this population. This defect introduces a premature termination signal, resulting in a deficiency of HEXA mRNA in affected individuals, most likely due to nonsense-mediated decay.\textsuperscript{10} Unlike other recessive diseases with a high incidence in a certain population (i.e. sickle cell anemia) no selective advantage of the heterozygous state has been conclusively proven. However, some believe that the heterozygous state
may confer some resistance to tuberculosis.\textsuperscript{11} The underlying reason for the current incidence and distribution of Tay-Sachs in the Ashkenazi Jewish population has provoked a large amount of debate in the field. Some argue that the geographical distribution of the disease is no different from any other disorder showing the signs of founder effect and genetic drift.\textsuperscript{12} There are others who cite the high frequency of other lysosomal storage disease among the Ashkenazi Jews as indirect proof that there must be some selection advantage conferred by this trait.\textsuperscript{13}

**Treatment**

At the present time there is no successful cure or treatment to halt the rapid progression of Tay-Sachs disease. A number of different therapies are being evaluated; however, none have proven effective in curing this devastating illness. Some of the potential therapies currently under study are enzyme replacement, bone marrow transplant, and gene therapy.

Enzyme replacement seems to be a logical solution to this problem and has recently received a great deal of attention. As mentioned earlier, Tay-Sachs leads to the storage of gangliosides, primarily in the lysosomes of neuronal cells. If the defective enzymes in the CNS could be replaced, this abnormal storage of gangliosides should be reduced. As simple as this may appear, it is far from an easy feat to accomplish. To be successful, this therapy would require not only that catalytically active HEXA reach CNS neurons, but also that defective cells be able to clear out the gangliosides that have already accumulated to recover a normal phenotype.\textsuperscript{14} While effective in non-neurological diseases of lysosome storage, enzyme replacement therapy is still not a viable option for Tay-Sach.\textsuperscript{15}

Bone marrow transplant is another therapy that shows promise in treating Tay-Sachs disease. Like enzyme replacement therapy, it has been able to correct similar enzymatic defects in visceral tissue, but the same problem remains with targeting the therapy to the CNS.\textsuperscript{16}

Another option that is currently being investigated is gene therapy. Gene therapy studies on mice with Sandhoff disease, which involves the loss of the $\beta$-chain of HEXA, have shown promise in decreasing inflammation and GM2-ganglioside buildup in the brain.\textsuperscript{17}

With no cure currently available for Tay Sachs, treatment is restricted to supportive care and the maintenance of comfort, by ensuring adequate nutrition and hydration, treatment of infection, and control of seizures. In severe cases bowel management is also a frequent problem.\textsuperscript{18}

**References**