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10/4/12
BioC 118Q
Disease Case Presentation

Tay-Sachs Disease

Tay-Sachs disease is heritable disease of the nervous system that is devastating in its deadliness. A progressive neurodegenerative disorder, this disease causes a steady loss of neurons in the central nervous system (CNS) until the disease leads to death, usually by age four or five in its most common form.[1] The genetic transmission of Tay-Sachs is autosomal recessive, so a child will have Tay-Sachs disease if he or she receives the defective gene from both parents. Though Tay-Sachs disease is very rare for the general population, it is more common for people of Ashkenazi Jewish descent (1 out of every 27 members are carriers[2]), as well as some Canadian communities of Quebec, the Old Order Amish community of Pennsylvania, and the Cajun communities of Louisiana.[3]

The disorder occurs because of a mutation in the alpha subunit of the HEXA gene on Chromosome 15. The HEXA gene has instructions for making a protein, hexosaminidase A, that becomes part of an enzyme that plays a critical role in the brain and spinal cord by breaking down a fatty substance called GM2 ganglioside. Because of the defective hexosaminidase A, the enzyme cannot work properly in order to break down the GM2 ganglioside, and the GM2 ganglioside builds up to toxic levels. That toxic buildup causes the destruction of neurons, which in turn, causes the manifestation of Tay-Sachs disease.[3] The speed of the progression of neuronal death, and in turn, symptoms of Tay-Sachs, depends on the amount of GM2 ganglioside buildup.[4] Tay-Sachs disease is known as a lysosome storage disorder because of that lethal buildup and because the enzyme is located in lysosomes, whose job is to break down and recycle substances not needed by the body. [3]

Tay-Sachs disease usually appears in early childhood (the infantile form), but there are rare occasions of Tay-Sachs disease occurring during childhood, adolescence, or adulthood. In the infantile form, the toxic buildup of GM2 ganglioside is so severe that it causes damage to the nerves even before birth.[2] The disease starts to take its toll and becomes apparent when the patient is 3-6 months of age and starts to become developmentally retarded: development slows, muscles and movement weakens, and motor skills, like crawling and sitting, are lost. As the disease progresses, it gets worse very quickly with the patient experiencing seizures, loss of hearing and vision, dementia, and paralysis until death by age two to five. If the disease appears in childhood or adolescence, which it very rarely does, the patient has many of the same symptoms as the infantile form, except less severe, with mental illness, weakness of muscles that are accompanied by ataxia, problems with speech, etcetera. For those who develop Tay-Sach's disease late in life, the symptoms vastly differ. [3]

Tay-Sachs disease is classically diagnosed by an eye examination or behavior observation. Ganglion cells in the eye are swollen with lipids (GM2 ganglioside), and those lipid filled ganglion cells leave a noticeable "cherry-red spot" on the eye that an optometrist can easily identify. Tay-Sachs is also identified when a person has an early, and then prolonged, reaction to sound, called the "startle reaction."[1] Other forms of diagnosis have been developed as well, such as finding swollen neurons in the CNS or an enzyme test measuring levels of the hexosaminidase protein.[2]

As of today, there is not yet a treatment for Tay-Sachs disease, only ways to make the patients more comfortable by dealing with the symptoms. Anticonvulsant medication is effective to control seizures when they first start occurring, and techniques are used to ensure proper nutrition and hydration.[5] Though there is no treatment yet, much research has arisen since finding

the defective HEXA gene on chromosome 15 in 1985. Blood tests have been developed, using either DNA analysis or an enzyme assay to identify Tay-Sachs carriers, and they have successfully identified 95% of carriers of Ashkenazi Jewish descent and 60% of the carriers within the general population.[6]

Because of carrier testing targeted specifically to the Ashkenazi Jewish population, the number of children born that develop Tay-Sachs has been so drastically lowered to the point in which Tay-Sachs disease now occurs more frequently in populations that are not thought to be high risk. As well, prenatal testing has been developed that tests a sample of placenta to identify if the fetus will have Tay-Sachs. Along with this, assistive reproduction has become a prevalent option for couples who are carriers but do not want to risk giving birth to a child with Tay-Sachs disease. In-vitro fertilization, along with testing the embryos for Tay-Sachs, allows the couple to implant normal embryos and give birth to only healthy babies.[6]

There is great promise in research for new therapies, the most prominent of which is to transfer a normal gene into cells of Tay-Sachs patients to replace the abnormal gene. This has proven successful in Tay-Sachs mice while improving Tay-Sachs cats. Clinical trials of this therapy for humans could potentially start as early as March 2013. Another therapy being explored is molecular chaperone therapy that is possibly being considered for patients with late onset Tay-Sachs disease, using pyrimethamine.[7] Molecular chaperon therapy uses molecular chaperones (small molecules able to cross the blood-brain barrier into the CNS) that can attach to a non-active enzyme in such a way to make the enzyme take on the correct shape to function. However, this therapy is challenging to figure out because pyrimethamine only responds to certain mutations (there have been more than 50 mutations identified on the HEXA gene that can cause Tay-Sachs disease[6]), and the wrong dose of the drug may actually make the disease worse

by lowering what activity the enzyme may have. Another option is a bone marrow transplant. However, it is a very invasive therapy and is only offered by two centers in the US. Of what surgeries have been done, this therapy has had very little success with Tay-Sachs patients.[7]

Tay-Sachs disease is a terrible disease, deriving from the progressive deaths of neurons that cause patients to suffer tremendously. With paralysis, ataxia, and mental retardation, the symptoms take a toll on the patients before death by age five in the infantile form and create much suffering for patients with late onset as well. There is no treatment, but there have been major gains in genetic testing to prevent the births of more children with Tay-Sachs disease, and gene therapy is being explored to help those patients that develop late onset Tay-Sachs disease. Though this disease is devastating, hopefully a treatment can be found in the promise that research on gene therapy is providing.

References

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