Tay-Sachs Disease

Yarl Dhayaparan

Period 6

June 3, 2013

Physiology

- It is an autosomal recessive disorder that skips generations.
- There is a deficiency of the Hex A gene, hexosaminidase A(a lysosomal enzyme) deficiency. It's unable to convert GM2 ganglioside (a type of lipid) to GM3 gangliosides and GM2s accumulate in myelin Nodes of Ranvier are unable to transmit signals.
- It manifests in those of primarily Ashkenazi Jewish descent, while Canadians, the Pennsylvania Amish and Louisiana Cajuns are also
- The three stages of onset: infantile, juvenile, and adult.
- Symptoms:Neurological deterioration, seizures, spasticity, ataxia and incoordination, vision loss, and psychiatric illness.
- Infantile onset: Begins ~ 3 to 6 mos. Most common and most LETHAL. Vision loss characterized by "cherry-red spot"
- Juvenile onset: Ataxia begins ~2 to 4 yrs.but spacticity + seizures manifest by 10-15 yrs. Vision loss, but not always a "cherry-red spot".
- Adult onset: Begins ~20s-30s. Psychiatric illness occurs. Vision loss doesn't always occur.

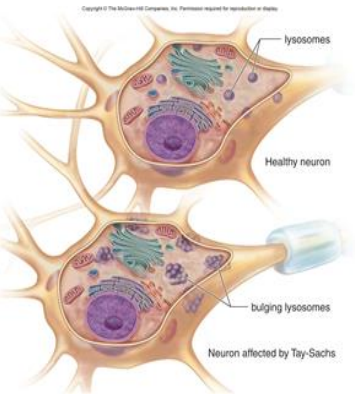


Figure 2

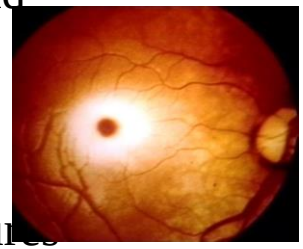


Figure 3

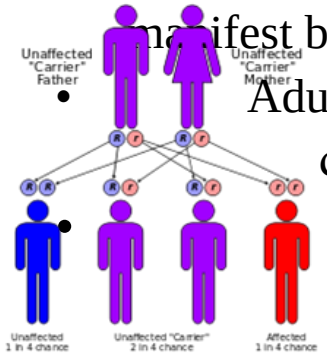


Figure 1

Molecular Cause

- Transmission: Autosomal Recessive Disorder; offspring must inherit two mutated alleles to be affected by TSD.
- There are 50 possible mutations, while only ~3 account for the mutated alleles of ~98% of these populations. These include point mutations, insertion and deletion of base pairs and splice set mutations.
- It is caused by a point mutation at 15q24.1 on chromosome 15.
- Most common mutation occurs in 80% of TSD patients. It's a frameshift mutation with T,A,T,C base pair insertion resulting in a premature stop codon.
- Overall effects of these mutations: GM2 gangliosides accumulate around nerve cells resulting in cell death

Figure 4

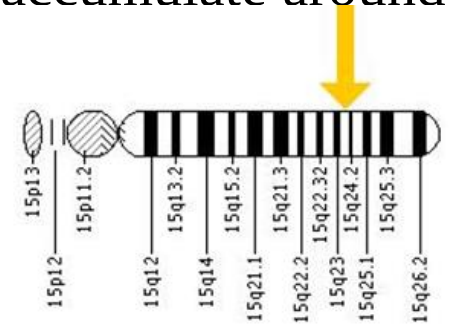
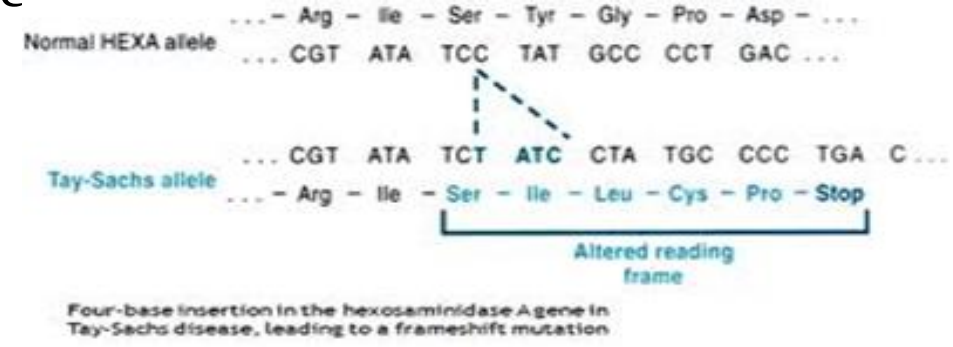


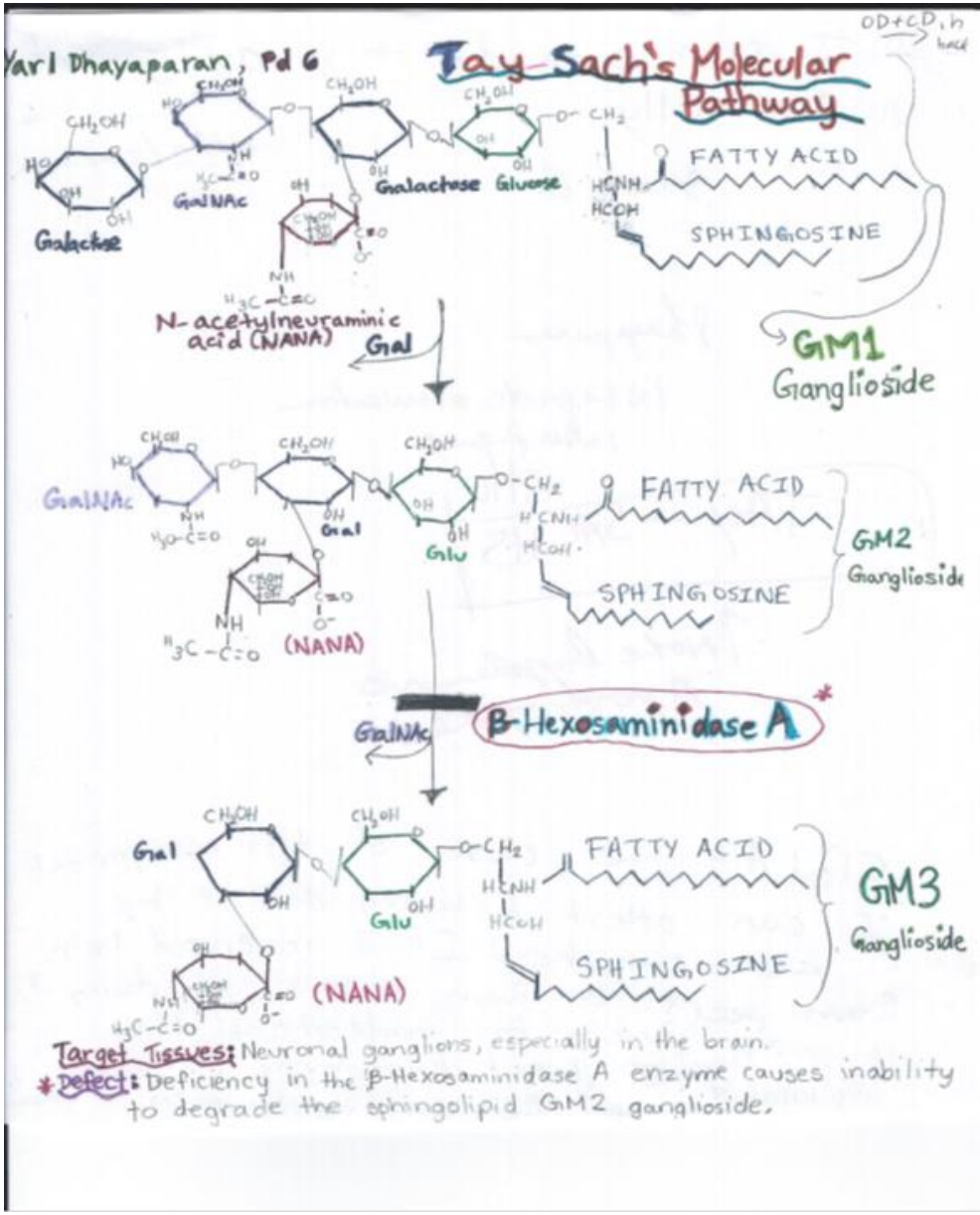
Figure 5



Four-base insertion in the hexosaminidase A gene in Tay-Sachs disease, leading to a frameshift mutation

Yarl Dhayaparan, Pd 6

Tay-Sach's Molecular Pathway



Target Tissues: Neuronal ganglions, especially in the brain.

***Defect:** Deficiency in the β-Hexosaminidase A enzyme causes inability to degrade the sphingolipid GM2 ganglioside.

Treatments/Risks and Limits

- TSD is a lethal disease.There is only symptomatic treatment available.
  - Anticonvulsive Medication to stop incidence of seizures.
  - Supportive Physical Therapy
  - Use of a feeding tube to aid swallowing

-There are antidepressants and antipsychotic meds for adult-onset patients. Unfortunately, the antipsychotic meds may not work for them and in rare cases lithium and electroconvulsive therapy. In extreme cases, patients may also be institutionalized in nursing homes and need ventilators.

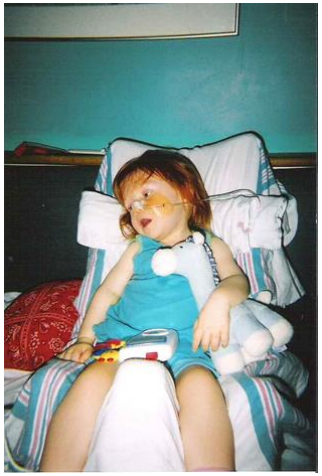


Figure 6

Limitations: Unfortunately, these therapies won't stop the progression of TSD. It is still LETHAL!!!.

Proposed Cure/Limitations

- One proposed therapy under study by The Hospital for Sick Children in Canada is to give later-onset Tay-Sachs patients the drug **Pyrimethamine (Daraprim).** Pyrimethamine crosses the blood-brain barrier and may act as a chaperone that is it binds to the active site of the Beta-Hexosaminidase complex and increases the enzyme activity. This is in Phase 2. Limits: Only tested on Juvenile-onset.

- **Enzyme Replacement therapy** has also been under study. It is when you separate the Hexosaminidase A enzyme from a vector (ex: plasmid) and inject the enzyme into a Tay-Sachs patient via IV infusion. An issue with this is that it is expensive and a repetitive process. Limits:Costly and repetitive.High chance of infection and a harmful immunological response and make the affected patient even sicker and weaken them. Studies have also shown that the enzyme is too large to pass the blood -brain barrier when it is injected directly into the blood.

- **Gene Therapy A.K.A. Viral Vector Mediator Gene Therapy** or inserting the entire HEXA A gene is being studied. Hypothetically, inserting a gene into diseased brain cells would correct the neurological defect. Limits:It worked in animal models such as mice and cats, but failed in humans.

My proposed Therapy

MY PROPOSED THERAPY: The most common mutation (80%)that causes Tay-Sachs disease is a frameshift mutation involving the insertion of the base pairs (T,A,T,C). I would excise these base pairs and place them in the coding region of DNA. It must be performed at an early stage of fetal development (to reduce neurological damage), you should remove an allele from a Tay-Sachs fetus using chorionic villi sampling (CVS). I would remove the four inserted base pairs using restriction enzymes. Then, you should ligate the sticky ends using DNA ligase. Then, inject the newly formed so-called normal Hex A allele into the nucleus of the brain cell of the fetus. In this approach, we would avoid the use of a vector and risk an immunologic response to the vector's antigens. Since this is performed in the individual's actual somatic cells,hypothetically, you would improve the success rate.

References

Physiology

- Thompson and Thompson 7th edition (2007):Tay-Sachs Disease
- htttp://www.glogster.com/michaelrixe/tay-sachs/g-6lio21utdij065t3ebs4ea0(Figure 1)
- http://static.wikidoc.org/5/58/Tay_Sachs_Retina.jpg (Figure 3)
- Kliegman, Robert. "86." *Nelson Textbook of Pediatrics.* 18th ed. Vol. 1. Philadelphia (Pa.): Elsevier Saunders, 2007. 593-95. Print.
- Zitelli, Basil J., and Holly W. Davis. "Chapter 19." 2002. *Atlas of Pediatric Physical Diagnosis.* 4th ed. St. Louis: Mosby-Wolfe, 1997. 684. Print.

Molecular Cause

- Thompson and Thompson 7th edition (2007) pg 210-212 (Figure 5 and info)
- http://ghr.nlm.nih.gov/gene/HEXA (Figure 4)
- Dill, Fred, Jan Friedman, Michael Hayden, and Barbara McGillivray. "Chapter 5."*genetics*:*The National Medical Series for Independent Study.* Baltimore: Harwal, 1992. 76. Print.

Treatments/Risks and Limits

- http://devonda-r-holmes.blogspot.com/ (Figure 4)
- Thompson and Thompson 7th edition (2007):Tay-Sachs Disease
- Kliegman, Robert. "86." *Nelson Textbook of Pediatrics.* 18th ed. Vol. 1. Philadelphia (Pa.): Elsevier Saunders, 2007. 593-95. Print.
- Zitelli, Basil J., and Holly W. Davis. "Chapter 19." 2002. *Atlas of Pediatric Physical Diagnosis.* 4th ed. St. Louis: Mosby-Wolfe, 1997. 684. Print.

Proposed Cure and Limitations

- Baker, Henry J., DVM, et al. "TAY-SACHS GENE THERAPY CONSORTIUM: A 3-year roadmap to a gene therapy clinical trial for Tay-Sachs Disease."*www.tsgtconsortium.com.* N.p., n.d. Web. 20 Mar. 2013.
- Dill, Fred, Jan Friedman, Michael Hayden, and Barbara McGillivray. "Chapter 5."*genetics*:*The National Medical Series for Independent Study.* Baltimore: Harwal, 1992. 76. Print.
- Hamilton, Richard J. "ANTIMICROBIALS: Antiviral Agents." *Tarascon Pocket Pharmacopoeia.* 14th ed. Burlington, MA.: Jones & Bartlett Learning, 2013. 40. Print.