Tay Sachs Disease

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1. Introduction
2. Signs & Symptoms
3. Epidemiology
4. Risk Factors
5. Inheritance
6. Pathophysiology
7. Diagnosis
8. Treatment
9. Conclusion
What is Tay Sachs?

- Rare genetic disorder
- Deletion of Hex A enzyme
- Destroys the nervous system in a progressive manner

(GHR, 2012)
SIGNS & SYMPTOMS
What to look out for
Early/Infantile Onset (~6 months)

- Mild muscle weakness
- Myoclonic jerks/twitches
- Acoustic hypersensitivity
  - Easily startled in response to unexpected noises
- Inability to hold eye contact
- Gradual loss of vision
  - “Cherry red spots” → macular cell degeneration caused by choroid exposure
  - Apparent in ~90% of Tay Sachs cases (NORD, 2016)
Childhood Onset (~2-10 years)

- Lack of coordination and motor skills
  - Clumsiness
  - Unable to walk properly

- Reduction in intellectual abilities

- May develop retinitis pigmentosa
  - Degeneration of the retina

- Loss of speech

(NORD, 2016)
Late Onset (Adolescence--)

- Reduction in motor coordination
  - Muscle weakness
  - Involuntary muscle contractions
  - Tremors

- Slurred speech

- Changes in mood and mental health

- Unable to complete daily tasks

(NORD, 2016)
EPIDEMIOLOGY

Distribution and determinants of Tay-Sachs disease
Genetic Risk Factors

Individuals of the following ethnicities are at a higher risk for being affected by Tay-Sachs or being heterozygous for the mutated allele:

- Ashkenazi Jewish
- French-Canadians of Quebec
- Old Order Amish in Pennsylvania
- Cajuns of Louisiana
- Family history of condition

(Koeslag, 1984)
Theories

- Heterozygote advantage
  - Being a carrier of mutated gene provides resistance against tuberculosis

- Random genetic drift
  - Change in allele frequencies due to chance

- Founder effect
  - Isolated populations
  - Small initial population: high genetic mutation frequency

- Reproductive compensation
  - Parents who have children affected by Tay-Sachs may continue reproducing

(Withrock, 2015)(Chakravarti, 1978)
Case Study

A couple has a female child with Tay-Sachs disease, and three unaffected children. Neither parent nor any of the biological grandparents of the affected child has had this disease.

- Dominant or recessive?
- Autosomal or X-linked?

(The University of Arizona, 1998)
PATHOPHYSIOLOGY

Underlying Mechanisms of Disease
Neurophysiology

- Central Nervous System
  - Brain & Spinal Cord

- Gangliosides
  - Plasma Membrane
  - Cell-cell recognition, adhesion and signal transduction
  - GM2 gangliosides

(Yu, Tsai, Ariga, & Yanagisawa, 2013) (Sandhoff & Harzer, 2013)
HEXA Gene

Chromosome 15

15q24.1

Encodes

β Hexosaminidase A

(Genetics Home Reference, 2017)

(Neudorfer et al., 2005)
Beta Hexosaminidase A

- Lysosomal Enzyme
  - Degrades GM2 gangliosides

- Two subunits
  - $\alpha/\beta$ heterodimer

- Tay-Sachs Disease
  - $\alpha$ - subunit

(Sandhoff & Harzer, 2013) (Myerowitz, 1997)
Cellular Pathway

(Sandhoff, 2013)
Mutation

- Single Point Mutation
  - Affect Lysosomal Catalytic Activity

(Pymol, 2009)

(Chavany & Jendoubi, 1998)

(Genetics Home Reference, 2017)

(Myerowitz, 1997)
Result

- GM2 Gangliosidosis
  - Neural Degeneration

(Sandhoff, 2013) (Sandhoff & Harzer, 2013)
DIAGNOSIS
Various screening methods
Diagnosis

- **Blood tests**
  - Measures hexosaminidase A levels in the body
  - Reduced levels in people with Tay-Sachs

- **Molecular genetic testing**
  - Detect mutation in *HEXA* gene

- **Testing prenatally**
  - Chorionic villi sampling (CVS)
  - Amniocentesis

(NIH, 2011) (NORD, 2016)
Carrier screening in schools

Figure 3. Test uptake for TSD carrier status. The proportion of students who had a carrier test was 84.9\% (N = 163) with blood sampling, whereas 96.0\% (N = 214) of students accepted testing with a cheekbrush; $\chi^2 = 15.2$, $df = 1$, $P < .0001$. 

(Gason et al., 2005)
TREATMENT

Treatment aimed at relieving symptoms
Treatment Approach

- Drug Treatment
- Genetic Counselling
- Psychosocial Support
Current Therapeutic Options

**Anticonvulsants**
- Anticonvulsants may be used to treat seizures
- Miglustat (synthetic analogue of D-glucose)

**Substrate Deprivation**
- N-butyldeoxynojirimycin (inhibitor of glycosphingolipid synthesis)

**Nutritional Support**
- Infants monitored for proper nutrition and hydration
- Feeding tube may be necessary

(Osher et al., 2011)
Investigational Therapies

Substrate Reduction Therapy (reduces production of accumulated substance)

Relieving symptoms and providing psychosocial support

Drug Treatment (Pyrimethamine) - Clinical Trials

Accumulated GM2 ganglioside

(Cachón-González et al., 2006)
Investigational Therapies...cont’d

Gene Therapy

Defective Lysosomal Enzyme

Enzyme-Replacement Therapy

Chaperone Therapy

(Cachón-González et al., 2006)
Conclusion

What can we do moving forward?
Family Battles Tay-Sachs Disease
National Tay-Sachs & Allied Diseases Association

4 key areas of focus:

- Education
- Advocacy
- Research
- Family Services
Questions

1. How is this disease inherited?
   a. Autosomal Dominant
   b. **Autosomal Recessive**
   c. X-linked Dominant
   d. X-linked Recessive

2. What gene is mutated in Tay-Sachs Disease?
   a. HEXA gene
   b. HEXB gene
   c. GM2 ganglioside
   d. β Hexosaminidase A
Thanks!

Any questions?


