MILLER-DIEKER SYNDROME

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PHYSIOLOGY

- Very rare disorder. The prevalence is unknown.
- Early onset. Usually lethal by age 2
- Lissencephaly: smooth brain with few wrinkles and folds. Less surface area
- The smoother the brain is, the more severe the symptoms are.
- intellectual disability and developmental delay
- Spasticity (abnormal muscle stiffness)
- Hypotonia (weak muscle tone)
- Feeding difficulties
- Seizures
- Distinct facial features
  - prominent forehead
  - midface hypoplasia (sunken at the middle of the face)
  - small and up-turned nose
  - up-turned eyes
  - low-set and abnormally shaped ears
  - a thick upper lip
  - hypertelorism (increased distance between the eyes)
  - a small jaw
  - a cleft palate
- rarer symptom: organ damage
  - Heart malfunction
  - Kidney malfunction

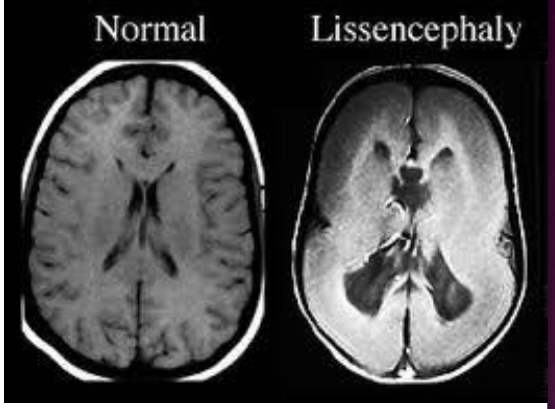

Figure 1

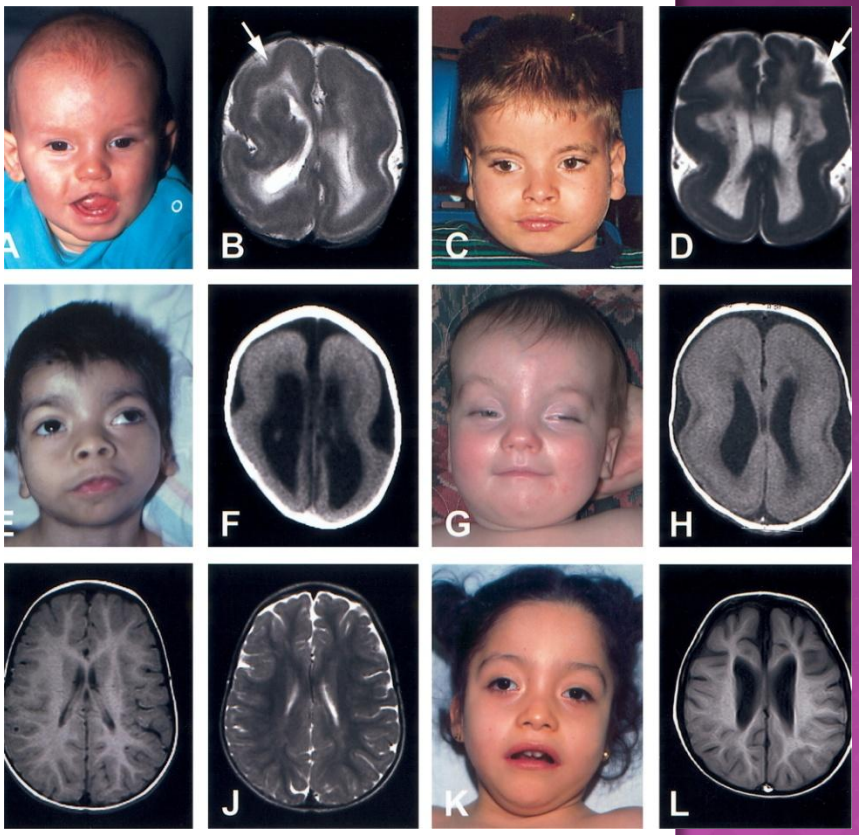

Figure 2

MOLECULAR CAUSE

- Caused by a deletion in the short p arm of chromosome 17, located at 17p13.3
- Deletion of the platelet-activating factor acetylhydrolase 1b, regulatory subunit 1 gene (PAFAH1B1 gene) causes lissencephaly.
- PAFAH1B1 genes makes the protein that is part of a complex known as the platelet-activating factor acetylhydrolase.
- This complex determines the number of platelet activating factor (PAF) molecules are in the body.
- PAF molecules are directly related to the movement of nerve cells in the brain
- It interacts with the microtubules in the cells (this process is referred to as neuronal migration).
- The protein expands and contracts the cytoskeleton by interacting with the microtubules that make up the cytoskeleton around the nucleus.
- The deletion of this gene would mean that these protein do not get produced and the microtubules would be unable to contract and expand to move the neurons in the brain.
- Another gene is the tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon polypeptide gene (YWHAE gene).
- This gene helps make a protein that regulates cell division and directs the movement of nerve cells in the brain.
- However, when there is a deletion of this gene, the symptoms of lissencephaly are observed to be much more severe.

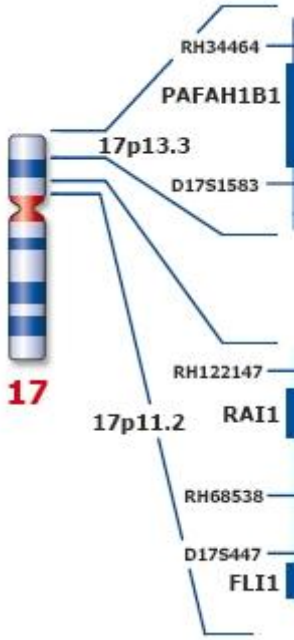

Figure 3

CURRENT TREATMENTS

- No Cure
- Can be detected early using prenatal ultrasonographic imaging to look for abnormal brain development in the fetus. It can also be detected by doing a CT or a MRI scan of the brain
- Evaluation from specialists: developmental evaluation, otolaryngology evaluation, cardiology evaluation, urology evaluation
- treatment for possible seizures: seizure medications
  - Limitation: seizures can occur at unpredictable times
- spasticity (muscle stiffness):
  - aquatic therapy and physical therapy
    - Helps with motor skills
- chewing and swallowing problems due to neurological delays
  - Surgery: place a gastrostomy tube between the stomach and the outside of the abdomen
    - patients can be directly fed and given nutrients through this tube
    - used to maintain a healthy diet
    - monitor how much food and nutrients

PROPOSAL

- Research done by the University of California in Los Angeles for Parkinson's disease
- Gene therapy: taking a normal gene and inserting it into a nonspecific location in the genome to replace a nonfunctional gene. A vector (the carrier molecule), usually viruses, is used to deliver the gene into the patient's target cells.
- Until recently, we have had problems getting the gene into the neuron cells because the viruses are usually too big.
- We can get the genes into the brain: fatty sphere called liposomes.
- The liposomes are coated with a polymer called polyethylene glycol (PEG).
- This polymer allows antibodies that usually go to certain neuron receptors to stick to a few PEG strands as well.
- The antibodies attached to the PEG strands trick the receptors to allowing the liposomes to pass onto the brain cells.
- This approach has already proven to be effective against rats and certain species of primates due to research done by the team in the University of California in 2000.
- This research shows some success with Parkinson’s disease. It might also work with Miller Dieker patients since both are neurological disorders.
- This procedure could possible allow us to reintroduce the PAFAH1B1 gene into MDS patients and allow the patients to continue to produce proteins that will allow their neurons to move normally.
- **Limitations**
- The immune system in our body tries to attack and rejects any foreign objects that is introduced into the human tissue.
- The liposomes deliver the genes to organs other than the brain.
- The blood-brain barrier.

REFERENCES

- **Physiology Slide**

Context

Genetics Home Reference (March 4 2013). Miller Dieker Syndrome. Retrieved from http://ghr.nlm.nih.gov/condition/miller-dieker-syndrome

Images

Facial Features (Figure 2)
http://drugline.org/medic/term/miller-dieker-syndrome/

Lissencephaly (Figure 1)
http://www.hxbenefit.com/lissencephaly.html

- **Molecular Cause Slide**

Context

Genetics Home Reference (March 4 2013). Miller Dieker Syndrome. Retrieved from http://ghr.nlm.nih.gov/condition/miller-dieker-syndrome

Genetics Home References (March 18 2013). YWHAE gene. Retrieved from http://ghr.nlm.nih.gov/gene/YWHAE

Healthline (2002). Miller Dieker Syndrome. Retrieved from http://www.healthline.com/galecontent/miller-dieker-syndrome

Images

Chromosome (Figure 3)
http://www.kreatech.com/products/repeat-freetm-poseidontm-fish-probes/microdeletion/5-tests-miller-diekerlissencaphaly-lis1pafah1b1.html

- **Treatments/Risks and Limits Slide**

Context

FDNA (March 19 2012). Miller-Dieker Syndrome. Retrieved from <http://fdna.com/resource-center/conditions-and-diseases/millerdieker-syndrome

8. Orphanet (September 2003). Miller Dieker. Retrieved from <http://ghr.nlm.nih.gov/condition/miller-dieker-syndrome>

9. WebMD (2012). Epilepsy drugs to treat seizures. Retrieved from <http://www.webmd.com/epilepsy/medications-treat-seizures>

- **Proposed Cure/Limits Slide**

Context

US National Library of Medicine National Institutes of Health. Tyrosine Hydroxylase Replacement in Experimental Parkinson's Disease with Transvascular Gene Therapy. Retrieved from
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC539333/