“The boy had been healthy until age 14 months, when he suffered a mild bout of diarrhea. A few hours later his body went limp. He never regained control of his muscles.”
Glutaric Acidemia 1: Overview

- Inherited metabolic disorder
  - Old Order Amish, 1970s
- Defective metabolic enzyme (glutaryl-CoA dehydrogenase) →
  toxic products in cells, esp. glutaric acid (top left)
- Key: ages 6 months to 5 years
- Stress/illness → sudden brain damage & nervous system injury
  - Often fatal, may be progressive
Classical Symptoms: A Sudden Killer

I. Before crisis (~healthy):
   - Unusually large head (macrocephaly)
   - High glutaric acid in urine

II. Sudden encephalopathic crisis
   - 6 months to 5 years of age
   - Damage to the basal ganglia (Goodman et al. (1995)) within hours
   - Preventable, but permanent once it has occurred

III. After crisis:
   - Movement disorders, paralysis, spasms, jerking, weakness
   - Body damaged for life; intellect may remain intact

http://www.nature.com/ejhg/journal/v14/n12/images/5201700f4.jpg
Key:
Avoid sudden brain damage before age 5

- After this age, the brain is more resistant to sudden damage
- Once damage has occurred, it is more or less permanent
- This is the main goal of diagnosis/treatment
Classical Diagnosis & Treatment

• **Diagnosis of GA1:**
  - **Examine urine** for excess glutaric acid and 3-hydroxyglutaric acid (GC/mass spectrometry)
    - Prenatal diagnosis
  - Confirmed by a deficiency of glutaryl-CoA dehydrogenase in cultured fibroblasts

• **Treatment—prevention:**
  - **Diet control**—Low lysine/tryptophan
  - Carnitine & riboflavin supplements
  - Aggressive management of fevers, vomiting, etc.
  - Brain injury rate 85-94% ➔ 35% (Strauss et al. (2003))
Molecular Genetics

- Autosomal **recessive** (Mendelian)
- Defect in **GCDH gene** coding for glutaryl-CoA dehydrogenase
  - Chromosome 13
- >38 different mutations (Zschocke et al. (2000))
- Old Order Amish
  - 10% carrier frequency
- Worldwide: 1 in 100,000 infants
- High penetrance; variable expressivity

Source: Genetics Home Reference
Genetics, Diagnostics, & Therapies

I. Genetics ➔ better diagnostics?

• Yes—sequence analysis of the entire coding region (offered by 13 of 32 labs) can verify presence of the disease

• Carrier testing (13 labs)

• Prenatal diagnosis (14 labs)

II. Genetic information ➔ new therapies?

• Therapies not yet tailored toward specific genetic information, but genetics aid diagnosis, which is paramount to treatment

Laboratory information: GeneTests
References & Resources

- OMIM:
- Genetics Home Reference: