Efficacious and Sustained IV Gene Therapy of Canavan’s Disease - The White Matter Does Matter

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CANAVAN DISEASE (CD)

- Genetic defect
  - Rare autosomal recessive mutations (> 50 identified) in AspA gene (1/6,400-135,000 people primarily with Ashkenazi Jewish heritage)

- Biochemical defect
  - Loss of AspA enzyme activity
  - N-acetyl aspartic acid↑ (NAA) in the CNS and urine

- Fatal neurological disorder
  - White matter degeneration
  - Hydrocephaly/leukodystrophy
  - Psychomotor defect
  - Early death
  - No treatment available
Molecular Etiology of the Disease

Neuron Oligodendrocyte

Neuron

Oligodendrocytes

L-aspartic acid

acetyl-CoA

N-acetylaspartate

aspartate

$3\text{Na}^+$

$\text{NAA}$ transporter

$\text{NaC}3$

acetate

aspartoacylase

L-aspartic acid

N-acetylaspartate

$3\text{Na}^+$

$\text{NAA}$
GENE THERAPY OF CANAVAN’S DISEASE - AN ATTRACTIVE THERAPEUTICS

- CD gene therapy trial with the 1st generation of recombinant adeno-associated virus (rAAV) vector in early 2000 by Mathew During and Paola Leone
  - Multiple site intracranial injections through 6 burr holes
  - Limited clinical improvement

- Challenge
  - Diffused white matter degeneration throughout the CNS requires wide-spread global CNS transduction
KEY ELEMENTS IN GENE THERAPY RESEARCH

- Gene delivery vehicle (i.e. vector)
- Method of vector delivery
- Therapeutic gene (e.g. AspA)
- Bona fide animal model for the disease
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