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Paul Wuh-Liang Hwu

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Gene Therapy for Aromatic L-Amino Acid Decarboxylase Deficiency

Wuh-Liang Hwu
National Taiwan University Hospital,
Taipei, Taiwan
AADC deficiency

AADC: aromatic L-aminoacid decarboxylase
5HIAA: 5-hydroxyindoleacetic acid
MHGP: 3-methoxy-4-hydroxyphenyglycol
VMA: vanilmandelic acid

3-O-MD: 3-O methylldopa
HVA: homovanillic acid
Clinical presentation of AADC deficiency

- Hypotonia (dopamine)
  - Axial hypotonia, limb hypertonia, decreased spontaneous movement, failure to make motor acquisitions
- Oculogyric crisis (dopamine)
  - Eye deviation upward, convergent, or to one side.
  - Prolonged (hours)
  - Opisthotonus with tonic or dystonic posturing of limbs
- Dystonia (dopamine)
- Autonomic system (catecholamines, serotonin)
  - Excessive diaphoresis, temperature instability, nasal congestion, Ptosis, miosis
- Mood and sleep (serotonin)
- Cognitive functions?
Clinical presentation of AADC deficiency

- Hypotonia and oculogyric crisis
AADC gene therapy

AAV2-hAADC

Bothering DOPA to AADC

AADC

5-OH-tryptophan

Serotonin

SN Tyrosine

DOPA

DA

Uptake

Signals

Putamen
Results

• Surgery
  – No intracerebral hemorrhage

• Cautions
  – Difficult stereotaxic surgery on small children
  – Poor pretreatment patient condition
  – Difficult posttreatment care

• Benefit
  – Initiate motor development
  – Increase in signal in FDOPA PET
  – Elevation of CSF neurotransmitter conc.
Case 1: 3m post gene transfer
Case 1: 7 months
Case 1: 19 months standing
Motor development after gene transfer

![Graph showing motor development over time for four patients.](image)
6-[^{18}F]fluorodopa PET – Patient 4

Before

6 months after
Current status of AADC gene therapy

• Compassionate use (Phase 0)
  – GMP production
  – 6 patients (2-6 yr) with critical condition
  – Good result

• Phase I trial (IND)
  – Depends on the good result from CU
  – GMP production required
  – Toxicity test required
  – Scheduled second season 2012
Conclusion

- Advantage of this gene therapy
  - Clear disease pathogenesis
  - Safety and efficacy of AAV2-hAADC has been demonstrated

- Difficulties – an ultra rare disorder
  - Lack of funding
  - Difficult regulation
  - Low interest to the Journals

- Driving forces
  - Many patients in Taiwan
  - A fatal disease with no treatment
  - Gene therapy is very effective
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