Update on Research in Alexander Disease
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Alexander disease: where are we?

- mutations in GFAP in ~95% of patients - dominant
- prevalence ~ 1 in 2.7 million (Yoshida et al. 2011)
- wide variation in clinical severity
- onsets at all ages (prenatal through 60’s)

- major questions:
  1. how do mutations cause disease?
  2. what accounts for the variability?
  3. what are the options for treatments?
topics

• sources of variability
  - environmental vs. genetic

• status of drug treatment studies
  - ceftriaxone and glutamate transport
  - Tecfidera (BG-12) and the Nrf2 stress pathway
Anne B. Johnson, M.D.  
(1927-2015)

- Cornell University, B.A., 1948
- Cornell Medical School, M.D., 1951
- internships, residencies, fellowships, and children
- Albert Einstein College of Medicine, Assistant to Associate Professor in the Departments of Pathology and Neuroscience, 1970-2002

- pioneer in Alexander disease research
- the first to document GFAP in the core of Rosenthal fibers
- played a key role in the discovery of GFAP mutations as the cause of the disease
environmental modifier - alcohol?

- 32 yr old male, previously healthy
- consumed 3 L beer + several spirits ("more than his usual")
- found prone, unable to stand or speak
- next morning eyes open and movable, but still couldn't speak or move limbs
- MRI features diagnostic for AxD, including tadpole sign in brainstem
- de novo 9 bp duplication-insertion in exon 1

- 3 mo. later - walking with cane, mild spasticity, psychomotor deficits
summary of genetics

- GFAP mutations account for >90% of patients
- all heterozygous, mostly de novo
- two hot spots at R79 and R239
- dominant, gain of function
- null or recessive mutations not found
- penetrance nearly 100%

monozygotic twins

- boys, R79H
- hypotonia, dystonia - first months
- sitting - 12 mo, 25 mo
- first words - 3 yr, 4 yr
- walking - 3.5 yr, 6 yr
- plateau - 6 yr
- loss of speech and unsupported walking - 8 yr
- wheelchair dependent - 10 yr

(Meins et al., 2002)
monozygotic twins

- boys, R79C
- developmental delays - 1 yr
- febrile seizures, then persistent - 1.5 yr
- macrocephaly, spasticity, pyschomotor and developmental delays
- independent walking - 2 yr

(Shiroma et al., 2003)
monozygotic twins

- boys, L235P
- onset (malnutrition, regurgitation) - 3 yr
- macrocephaly, seizures - no
- spasticity, ataxia - yes
- bulbar/pseudobulbar signs - yes
- cognitive deficits - no
- atypical MRIs (focal bulbar lesions)
- died - 8 yr, 10 yr

(Li et al., 2005)
mouse strain variation in GFAP response and the search for genetic modifiers

Hippocampus

Cortex (parietal)

ng GFAP / mg protein

ng GFAP / mg protein

FVB/N
129S6
C57BL/6J
FVB/N
129S6
C57BL/6J

wild-type

R236H

(Hagemann, unpublished)
glutamate transporters as therapeutic targets

glutamate transport into astrocytes may be affected in AxD

- Glt-1 is a major glutamate transporter, primarily found in astrocytes
- Glt-1 expression is reduced in hippocampus in mouse models
- Comparable findings in human tissues

Ceftriaxone - our experience

- No increase in expression:
  - alphaB-crystallin
  - Nrf2
  - Glt-1 transporter

- Hence, we have no data to support its use in humans

Survival of GFAP Tg;GFAP +/R236H mice

- Saline (n = 2)
- Ceftriaxone (n = 6)
- No injection (n = 11)

Lab meeting 5/18/11
is Nrf2 a useful target?

- Nrf2 is a transcription factor that regulates expression of many other genes
- Nrf2 is activated in both mouse and human AxD
- we tested whether forcing astrocytes to make even higher levels of Nrf2 is beneficial

Results

- reduces accumulation of GFAP
- reduces or eliminates Rosenthal fibers

LaPash Daniels CM et al., *J Neurosci* (2012)
forcing astrocytes to make more Nrf2 reduces GFAP

LaPash Daniels CM et al., *J Neurosci* 32, 10507 (2012)
dimethyl fumarate (BG-12) is an activator of Nrf2
BG-12 recently approved for use in MS

- but should this be tried in Alexander patients?
  1. questions remain about how much gets into the CNS, and whether it really activates Nrf2
  2. we do not know anything about dosing for children, and how to measure efficacy
  3. unfortunately, animal studies are no longer possible
  4. nevertheless, this is being tried in at least one or two patients

3rd Oral Drug to Treat MS Is Approved by the F.D.A.

By ANDREW POLLACK

A chemical once used to treat sofas — until it was found to cause rashes and blisters in people who sat on them — is now poised to become a major therapy for multiple sclerosis.
summary

• sources of variability
  - environmental vs. genetic (both are subjects of current investigation)

• status of drug treatment studies
  - ceftriaxone - mouse studies were done, but the results were negative
  - Tecfidera (BG-12) - mouse studies are not possible