ALS Neuropathology and Spread: Synchronization, Desynchronization, and Saturation

VA National ALS Brain Bank Neuropathology Meeting
Zoom
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Topics to be discussed

- Prime attributes of ALS onset and progression
  - Focality
  - Stochasticity
  - Neuroanatomic propagation (spread)
- Implications
- Respiratory constraints
- Implications of temporal-spatial summation
  - Neuropathology
  - Genomics
ALS phenotypes: Continuous variation formalized in a scheme

ALS focality, stochasticity and spread

Differences lead to “desynchronization”

Prime determinants
1. Focal
2. Stochastic
3. Converging network (hypocenter & epicenter)
4. Variably distributed between cortex (UMN) & spinal cord (LMN)
5. Contiguously and independently spreading
6. Variable kinetics

Ravits et al., 2009
Neurodegeneration is sequential and summating in contiguous compartments. Ravits, Exp Neurol, 2014.

Finite post-mitotic compartment with temporal-spatial summation.
Propagation in ALS: Alternative Models

Braak H, Brettschneider et al, 2013

Kanouchi, Ohkubo, & Yokota, JNNP, 2012

van den Heuvel et al, J Neurosci, 2011

Smith RA et al, Medical Hypotheses, 2015
# Motor Anatomy of Respiration

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<th>ID</th>
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| 55M JM  | Neck drop, shoulder/scapular weakness, and respiratory, ?FTD             | Limb ALS (high cerv), phrenic LMN>>UMN, but FTD | Onset: Sept, 2013
| 30106600| Onset: Sept, 2013                                                        | Course: >2 years            | Exam: LMN>>UMN, ?FTD                                                                 |
|         | Exam: LMN>>UMN, ?FTD                                                    | FRS: 30/48                  |                                                                 |
| 74M RB  | Axial weakness, then generalizing incl. respiratory                      | Thoracic onset, intercostals LMN>UMN | Onset: Nov, 2014
| 30121577| Onset: Nov, 2014                                                        | Course: Dead at 1 yr        | Exam: LMN>UMN, axial & abdominal                                                                 |
|         |                                                                         | FVC: 50% at 9 months, 0% at 12 mos |                                                                 |

- Diaphragm muscle
- Phrenic nerve C3-5
- Intercostal muscles
- Intercostal nerves T1-12
- UMN
- Regulatory
1. Onset is random (stochastic) & focal; 
2. UMN & LMN loss converge on same body region (hypocenter & epicenter); 
3. Disease burden is variably distributed between UMN & LMN; 
4. Spread is contiguous and independent at UMN & LMN; 

ALS: Early vs Late Stages

Clinical onset

“End-stage neuropathology”
Neuropathological staging is relative.


Ravits et al, Neurology, 2007b