Amyotrophic Lateral Sclerosis (ALS)

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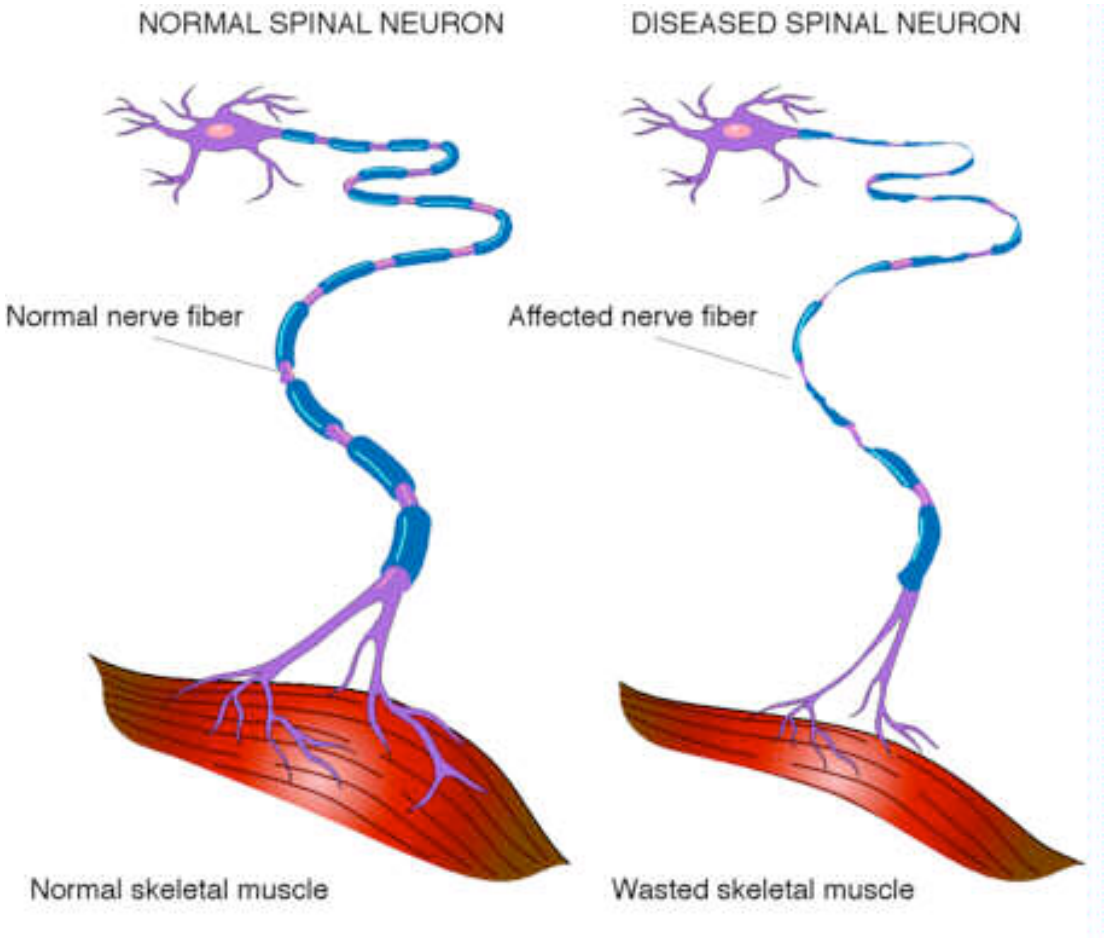
History of ALS

- 1874 – Jean-Martin Charcot
- 1939 – Lou Gehrig
- 1991 – Famililial ALS loci discovered

http://scienceniche.com/physical-science/scientist-and-researchers/jean-martin-charcot-neurologist29-november-1825-16-august-1893.html http://www.newworldencyclopedia.org/entry/Lou_Gehrig

Symptoms and Immediate Cause

- Microglial and astrocyte inflammation
- Death of motor neurons in brain, spinal cord, and brainstem
- Loss of coordination and strength
- No loss in mental acuity
- Death in ~3yrs



http://health.stateuniversity.com/pages/69/Amyotrophic-Lateral-Sclerosis.html

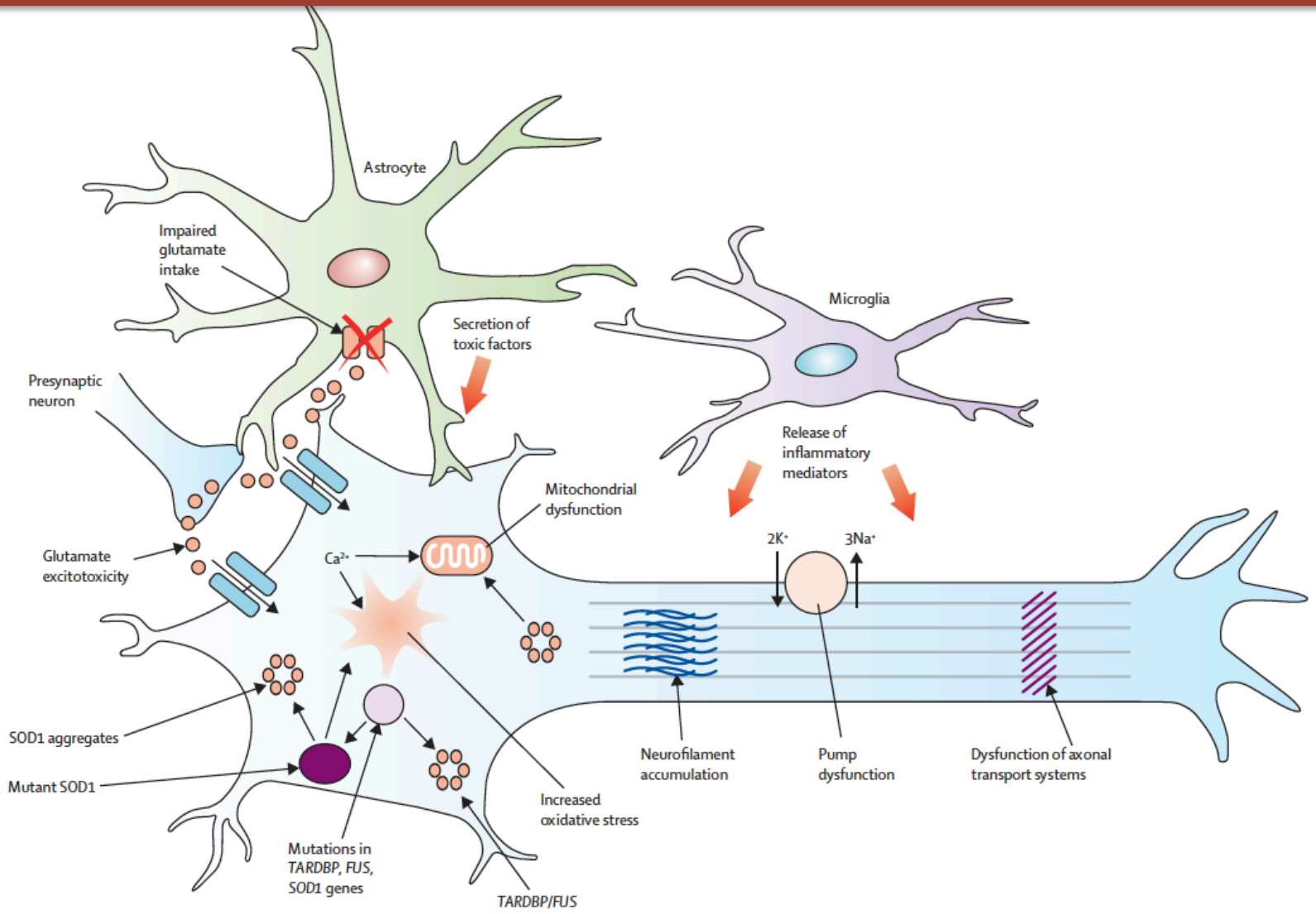
Clinical Types

- Familial forms (10%) and 13 Loci
  - SOD1 (20%)
  - TDP-43 (5-10%)
  - FUS (5%)
- Non-familial cases
  - family with other neurodegenerative disorders
- Environment
  - β-methyl-amino-L-alanine on Guam
  - high physical activity

Protein Involvement

- SOD1
  - protein aggregates
  - ROS
- TDP-43 and FUS
  - ubiquitinated cytoplasmic protein aggregates in all patients
  - RNA processing defect?

Pathogenesis



GWAS Studies – DPP6

- 1767 cases, 1916 controls
- 311,946 SNPs
- rs10260404
- intron 3 (C/T)
- $p = 5.04 \times 10^{-8}$
- OR=1.30
- Unknown reasons

GWAS Studies – KIFAP3

- 1800 cases, 2258 controls
- 288,357 SNPs
- rs1541160
- intron 8 (C/T)
- p=1.84x10-8, corrected p =.02
- survival advantage mean 14mo
- 50.4% TT, 39.7 CT, 9.9% CC
- Unknown reasons

GWAS Studies – UNC13A

- 2323 cases, 9013 controls
- 317K SNPs (variable)
- rs12608932
- intron 21 (C/A)
- $p = 1.30\ 10^{-9}$
- OR=1.25
- glutamate excitotoxicity, release of neurotransmitters

GWAS Studies – 9p21

- 599 patients, 4144 controls
- rs3849942
  - $p=2.22\times10^{-6}$
  - OR = 1.39
- rs2814707
  - $p=3.32\times10^{-6}$
  - OR = 1.38
- ORF unknown, reasons unknown

Controversy

- DPP6 has been refuted in 4 studies
- A few studies have tried and nothing has come up significant
- All done on European populations

Resources

- http://www.als-mda.org/publications/als/als5_6.html
- Amyotrophic Lateral Sclerosis, Kiernan MC *et al.,* The Lancet (2001)
- Reduced expression of the *Kinesin-Associated Protein 3* (*KIFAP3*) gene increases survival in sporadic amyotrophic lateral sclerosis, Landers JE *et al.,* PNAS (2009)
- Genome-wide association study identifies 19p13.3 (UNC13A) and 9p21.2 as susceptibility loci for sporadic amyotrophic lateral sclerosis, Van Es *et al.*, Nature Genetics (2009)
- Genetic variation in DPP6 is associated with susceptibility to amyotrophic lateral sclerosis, Van Es *et al.*, Nature Genetics (2008)
- Chromosome 9p21 in sporadic amyotrophic lateral sclerosis in the UK and seven other countries: a genome-wide association study, Shatunov A et al, Lancet (2010)