ALS

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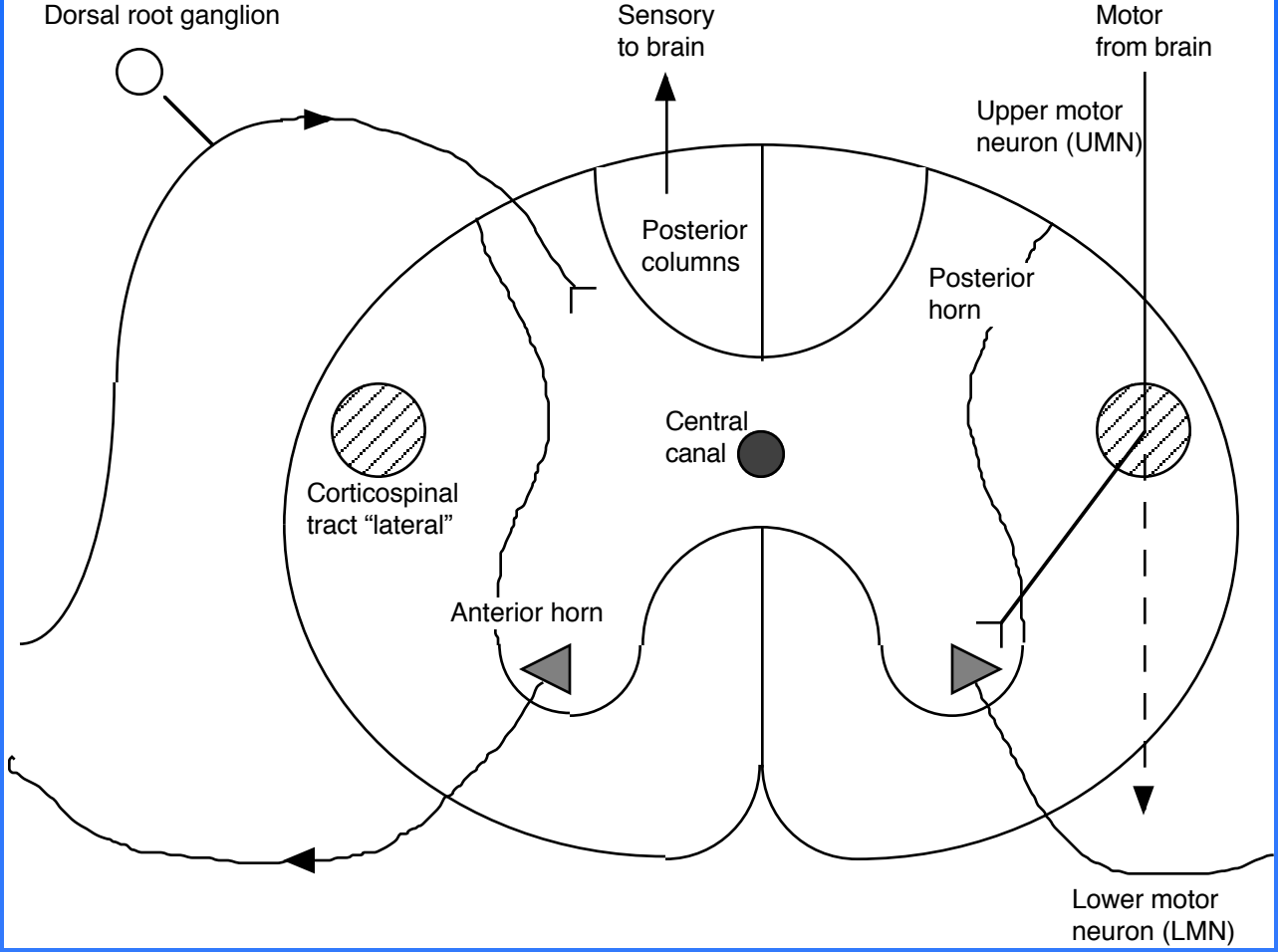
Neurology

Spinal Cord


Dorsal root ganglion
Sensory
to brain
Motor
from brain
Upper motor
neuron (UMN)
Posterior
columns
Posterior
horn
Central
canal
Corticospinal
tract “lateral”
Anterior horn
Lower motor
neuron (LMN)

Motor Neuron Diseases

- UMN only
  - Primary lateral sclerosis
- UMN and LMN
  - Amyotrophic lateral sclerosis (ALS or Lou Gehrig's dis.)
- LMN only
  - Spinal muscular atrophy
    - Infantile form (Werdnig-Hoffman)
    - Juvenile form (Wohlfart-Kugelberg-Welander)
    - Adult form (progressive muscular atrophy)
  - Spinobulbar muscular atrophy (Kennedy's dis.)
  - Viral infections
    - Poliomyelitis
    - HIV
    - West Nile
  - Rare paraneoplastic

ALS

- Epidemiology
  - 1/100,000 population
- Sporadic
- Variants
  - Frontotemporal dementia
  - Parkinsonism
  - Guam
- Familial
  - 5% of cases
  - Genetic testing available
    - C9orf72 (30%)
    - SOD1 = Cu,Zn superoxide dismutase (20%)
    - FUS = fused in sarcoma (4-5%)
    - TARDBP = TDP43 (5%)
    - Others

C9orf72

- Most common genetic mutation
  - ~30% familial (AD)
  - ~5% sporadic
- GGGGCC hexanucleotide repeat
  - Large 250-1600 repeats (normal <24)
- Unknown gene function on chrom 9p21
- High incidence of comorbid FTD

Case: Motor Neuron

This 58 year-old man first noticed right hand weakness 4 months ago. Three months ago he developed dysarthria and mild trouble swallowing liquids. One month ago he developed a left foot drop. All the symptoms are progressing. No pain or sensory loss is present.

ALS: Clinical

- No sensory, visual, or B/B involvement
- Asymmetric weakness
- Bulbar or limb onset
- Survival usually 2-5 years
- 30-50% develop dementia
  - Frontotemporal dementia type (FTD)

ALS: Clinical

- Upper motor neuron
  - Weakness
  - Increased reflexes
  - Spasticity
  - Pseudobulbar
  - Babinski sign (rare)
- Lower motor neuron
  - Weakness
  - Decreased reflexes
  - Atrophy
  - Fasciculations
  - EMG denervation

Clinical: Severe

ALS: Pathology

- 3 main features
  - Loss of anterior horn cells
  - Corticospinal tract degeneration
  - Loss of Betz cells in the cortex
- Additional findings may include loss of frontal or temporal cortical neurons (FTD).
- Inclusions
  - Neurofilament
  - Ubiquinated
  - TDP-43
  - Others

ALS: Etiology

- Unknown
- Hypotheses
  - Altered RNA processing
  - Glutamate toxicity
  - Free radical damage
  - Auto-immune
  - Viral (Enterovirus)
  - Mitochondrial
  - Growth factors
  - Apoptosis

ALS: Treatment

- Rehabilitative
- Medications
  - Riluzole is FDA approved
  - Symptomatic
- Gastrostomy tube
- Mechanical ventilation

- Symptomatic drugs
  - Amitriptyline
  - Baclofen/Zanaflex
  - SSRIs
  - Narcotics

ALS: Riluzole

Dynamed

Riluzole:

- American Academy of Neurology (AAN) recommendations on riluzole
  - riluzole recommended for slowing disease progression in ALS (AAN Level A)[3]
  - use riluzole 50 mg twice daily in patients
    - with definite or probable ALS of < 5 years duration
    - with forced vital capacity (FVC) > 60% predicted
    - without tracheostomy
    - Reference - Neurology 1997 Sep;49(3):657
  - consider withholding riluzole in those patients who develop fatigue as a side effect after discussing risk of fatigue vs. modest survival benefit (AAN Level C)[4]
- **riluzole 100 mg/day may prolong survival by about 2-3 months (level 2 [mid-level] evidence)**
  - based on Cochrane review with borderline statistical significance
  - systematic review of 4 randomized controlled trials of riluzole with 1,477 adults with ALS
  - comparing median survival with riluzole 100 mg vs. placebo
    - 15.5 months vs. 13.2 months in meta-analysis of 2 homogeneous trials with 631 patients (p = 0.042)
    - 14.8 months vs. 11.8 months in meta-analysis including third trial with 168 older patients with more advanced disease (p = 0.056), but limited by heterogeneity (p < 0.0001)
  - riluzole 100 mg associated with decreased mortality at 1 year in analysis of 3 trials with 799 patients (p = 0.0036, NNT 11)
    - risk ratio 0.78 (95% CI 0.65-0.92)
    - NNT 7-29 with 44% mortality in control group
    - results limited by significant heterogeneity (p = 0.05)
  - fourth trial from Japan with 195 patients had no significant differences in multiple clinical outcomes and did not report survival-specific data
  - riluzole associated with small but significant beneficial effect on bulbar and limb function but not on muscle strength in analysis of 3 trials with 731 patients
  - elevated serum alanine transferase (ALT) (> 3 times upper limit of normal), nausea, and asthenia significantly more frequent with riluzole
  - minimal data on quality of life
  - Reference - Cochrane Database Syst Rev 2012 Mar 14;(3):CD001447

END