Amyotrophic Lateral Sclerosis (ALS) — Grand Rounds

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Amyotrophic Lateral Sclerosis learning objectives

- 1. Recognize core epidemiology and common presentations of ALS.
- 2. Identify common reasons for delayed diagnosis and how to avoid them.
- 3. Review disease-modifying medications, their evidence and the value of multidisciplinary care.

Disclosures

- I have no disclosures.

What is Amyotrophic Lateral Sclerosis? (*Lou Gehrig's Disease, Motor Neuron Disease)*

- Progressive neurodegenerative disease affecting upper and lower motor neurons.
  - Including the motor elements of the bulbar cranial nerves

Epidemiology & natural history

- Incidence: ~1–3 per 100,000 person-years worldwide; prevalence 4–8 per 100,000
- Typical onset age 55–75; men slightly more affected; ~5–10% familial (SOD1, C9orf72 etc).
- Median survival 2–4 years from symptom onset.

Key exam findings to detect ALS

- Lower motor neuron: weakness, atrophy, fasciculations, decreased reflexes in affected muscles.
- Upper motor neuron: weakness, hyperreflexia, spasticity, pathological reflexes - Babinski sign, Hoffman’s sign, Jaw jerk
- Absence of sensory or autonomic findings

Common clinical presentations

- Limb-onset (70%): asymmetric distal/proximal weakness, cramps, fasciculations.
- Bulbar-onset (30%): dysarthria, dysphagia, emotional lability (pseudobulbar affect)
- Cognitive/behavioural: up to 40% may have frontotemporal dysfunction.
- Subtypes PLS, PMA, PBP

PseudoBulbar Affect

- A neurological condition causing sudden, uncontrollable episodes of laughing or crying that are often disproportionate to or inconsistent with a person's actual feelings
- 15-50% frequency
- Upper motor dysfunction of corticobulbar pathways
- Treatment Nuedexta (dextromethorphan/quinidine)

Diagnostic workup

- Electromyography (EMG) and nerve conduction studies — look for active denervation and chronic reinnervation in multiple regions.
- MRI brain/spine to exclude structural mimics (cervical myelopathy, mass lesions).
- Basic labs to exclude mimics: TSH, B12, HIV, syphilis, autoimmune panel as indicated.
- Consider neurofilament light chain(NfL) as a supportive biomarker (where available).

Mr. RH

- 76 yom
- Hypertension
- Hyperlipidemia
- Prediabetes
- Lung nodules
- Ex-smoker, rare EtOH
- Retired engineer
- Divorced, lives alone, 3 adult sons, brother USA

MRI Brain

- Mild/moderate generalized cortical volume loss , not suggestive of neurodegenerative process such as frontotemporal dementia
- Numerous white matter hyperintensities favoring moderate microangiopathic change
- Bilateral chronic lacunar infarcts,
- alternatively findings may relate to early vascular dementia –clinical correlation

- Neurology probable MND(ALS)
  - Referral Sunnybrook ALS clinic
  - Referral EMG
- Mayo clinic Rochester
- McMaster ALS clinic

Delayed ALS diagnosis

- 10 visits(2 phone), 4 physicians – diagnosis at 17 months

- Canadian Neurological Disease Register
  - Average time from symptom onset to ALS diagnosis is 21 months

Retrospectoscope

- Pseudobulbar Affect (emotional incontinence)
  (up to 50% ALS)
- Slurred speech (bulbar cranial nerve dysfunction)
  30% ALS with bulbar presentation
- Symptoms attributed to another diagnosis
  (depression, CVA, R/O malignancy, ENT disease)
- Weight loss(60% in ALS)
- Thorough neurological examination

Disease Modifying Therapies

- Multidisciplinary ALS clinics improve survival and quality of life.
- Early involvement: speech-language pathology (swallowing strategies), gastrostomy planning, nutrition.
- Respiratory monitoring (FVC). Non-invasive ventilation (NIV) prolongs survival and improves symptoms.
- Address advance care planning early, discuss goals, palliative care.

Riluzole(Rilutek)

- Glutamate modulating agent
- Dose: 50 mg orally twice daily (some protocols use 100 mg/day total)
- Grade 1A recommendation, approved since 2000
- Modest survival benefit (studies suggest ~2–3 months) real world evidence has demonstrated median 6-19 months survival benefit
- Mild GI side effects and dizziness, monitor LFTs
- Cost Cdn $5300/yr

Edaravone (Radicava)

- Free radical scavenger, antioxidant
- may slow functional decline (ALSFRS-R) for use in selected early-stage patients;
- 2B recommendation, oral formulation approved 2022
- Cost Cdn $123,000 1st year $119,600 subsequent years

Tofersen(Qalsody)

- First in class gene silencing for familial ALS (5-10%) those with the SOD1 gene, genetic testing if FHx
- Initial results showed 60% reduction of neurofilament light chains (VALOR trial) accelerated approval in 2023, data not yet translating to clinical benefit, ongoing ATLAS trial to 2027
- Iceland 2025, 4 patients -no deterioration, 3 of 4 showing improvement
- Intrathecal infusion q 2-4 weeks
- Cost…Cdn $425,000 1st year- $368,000 subsequent years
- Only 40 patients qualify

Key Takeaways (what I have learned)

- Think ALS (MND)with progressive asymmetric weakness
  - Look for UMN S/S and look for LMN S/S and look for Bulbar S/S (dysarthria/dysphagia) and PBA(emotional incontinence)
- Include ALS on DDX for unexplained weight loss
- Refer early to neurology, physiatry, EMG– “suspect ALS” may expedite.
- Early referral to multidisciplinary care ALS clinics at McMaster, Sunnybrook - survival and QOL benefit
- Disease modifying therapies exist with greater benefit if started early, ongoing clinical trials

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Questions?

UMN vignette 1: Brisk reflexes with wasting

- 62-year-old man with 6 months of progressive right hand weakness and visible interosseous wasting. Exam: marked atrophy and fasciculations, but reflexes are 3+ with a positive Hoffman sign.
  - Teaching point: LMN signs plus hyperreflexia in the same limb strongly suggest ALS rather than peripheral neuropathy.

UMN vignette 2: Pseudobulbar affect

- 70-year-old woman with progressive dysarthria and choking episodes. She has episodes of uncontrollable laughing that are incongruent with mood. Jaw jerk is brisk.
  - Teaching point: Emotional lability and brisk jaw jerk are classic UMN bulbar signs; think ALS or other UMN disease.

Questions?