When to consider a diagnosis of ALS

ALS overview[1–5]

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive motor neuron disease with an incidence rate of 2–3 per 100,000 per year. Its diagnosis is complicated by the lack of a validated diagnostic biomarker, highly variable initial clinical presentations, and multiple differential diagnoses. The difficulty of diagnosing ALS in Canada is evident in its mean time from symptom onset to diagnosis of **21 months**. ALS diagnosis is therefore based on both exclusion and clinical expertise—**early assessment in a multidisciplinary ALS clinic is essential to optimize clinical care**.

Diagnostic process

Patient History

Presentation

Cardinal ALS features: Progressive...

Articulation/speech difficulties (with normal investigations and no clear cause)

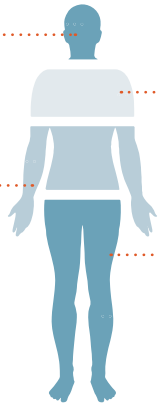
Limb weakness (with no pain/sensory deficit)

Shortness of breath (secondary to a neuromuscular cause with no evidence of respiratory disease)

ALS may present with any of the following signs/symptoms and functional deficits:

Head and neck (bulbar)[6,7]
- Slurred speech
- Pseudobulbar affect (emotional lability/incontinence)
- Difficulty swallowing
- Excess saliva

Upper body[6-8]
- Weakness resulting in a decline in fine motor function
  - Impaired handwriting
  - Difficulty with everyday tasks (e.g., preparing food, starting the car, using keys, opening jars or bottles, retrieving change from pockets, etc.)
  - Trouble with dressing/hygiene (e.g., doing buttons, cutting fingernails, etc.)



Respiratory[6]
- Shortness of breath with walking or ADLs
- Orthopnea (shortness of breath when supine)

Lower body[6-8]
- Weakness resulting in a decline in gross motor function
  - Frequent tripping
  - Difficulty on stairs, getting out of a chair, standing on toes, etc.
  - Foot drags when walking
  - One leg struggles to keep up with the other

Probing questions (derived from ALS literature)[8–11]

	Consider ALS	Consider alternative diagnosis
When did the symptoms start and what was the timing of onset?	**Gradual onset** (i.e., insidious; over the course of weeks to months)	Acute onset (i.e., over the course of minutes to hours)
Are there non-motor signs or symptoms (i.e., ocular, bowel, or bladder functions impacted)?	**No**	Yes
Are the symptoms progressive in the absence of any pain or sensory deficits?	**Yes**	No
Does anyone in their family have a history of ALS or another neurological disease with progressive weakness or cognitive impairment?	**Yes***	—

* 5–10% of patients have familial ALS; therefore, a "No" to this question should not exclude ALS.
ADLs, activities of daily living; ALS, amyotrophic lateral sclerosis.

Neurological Exam

Exam findings consistent with ALS[4,12–15]

	When to consider ALS	
Cognitive status	• Usually normal • May exhibit some frontal cognitive changes	• May show pseudobulbar affect
Cranial nerves	• Atrophy, fasciculations, and/or slowed movements of the tongue • Difficulties with speech and/or swallowing	• Facial weakness • Brisk jaw jerk
Motor exam	• Atrophy, fasciculations • Tone may be normal or spastic	• Myotomal distribution of weakness • Brisk reflexes
Sensory exam	• Normal	
Coordination	• Normal (accounting for spasticity or weakness)	
Gait	• High steppage gait • Spastic gait	

Differential Diagnoses

Where/what is the lesion?

Anatomical/etiological diagnosis[4,16]

ALS diagnosis is currently made using the revised El Escorial criteria and requires:

Presence of

- **Lower motor neuron (LMN) degeneration** by clinical exam and electrophysiological testing
- **Upper motor neuron (UMN) degeneration** by clinical examination
- **Progressive spread of symptoms or signs** within a region (i.e., brainstem, cervical, thoracic, or lumbosacral spinal cord) and to other regions, as determined by history or examination

Absence of

- **Electrophysiological evidence of other disease processes** that might explain the signs of LMN and/or UMN dysfunction
- **Neuroimaging evidence of other disease processes** that might explain the observed clinical and electrophysiological signs

A referral to a specialized ALS clinic and an MRI assessment **as soon as possible** is best for optimal care in patients for whom ALS is a diagnostic consideration.

- Patients can be referred to an ALS clinic even **while examination results are pending**—the specialist team at your regional multidisciplinary ALS clinic can provide timely appointments and will perform the necessary additional investigations to confirm the diagnosis.

ALS, amyotrophic lateral sclerosis.

Case study: Applying diagnostic flags for ALS to clinical practice

58-year-old active woman

Patient History

Presentation

JANUARY

Patient visits primary care physician as symptoms have not resolved.

Patient is referred to a physiotherapist as it is suspected to be an exercise-related injury.

MAY

Patient presents to neurologist with severe foot drop on the right side and complains of frequent and worsening issues with tripping and mobility (feeling unsteady). MRI (spine) is ordered.

DECEMBER

Following a long and challenging at-home workout, patient notices their right foot is dragging slightly on the ground while walking in the absence of any pain or sensory symptoms.

MARCH

Physiotherapy has no impact and foot drop has become more pronounced.

Primary care physician refers patient to a neurologist with suspected L5 radiculopathy or peroneal neuropathy.

AUGUST

MRI results unremarkable. Weakness in right leg has worsened and has spread to the left foot, which is now also dragging.

Onset? Gradual | **Non-motor symptoms?** No | **Progressive without pain or sensory deficits?** Yes | **Family history of ALS?** No

These flags rule out a herniated disc causing an L5 radiculopathy and can prompt consideration for a possible ALS diagnosis.

Neurological Exam

Cognitive status	• Normal
Cranial nerves	• Normal
Motor exam	• Bulk: Reduced in distal right leg, fasciculations observed in both legs • Tone: Normal • Power: L5 myotomal distribution of weakness in right leg (grade 3/5) • Weakness also observed in ankle dorsi-flexion in left leg (grade 4/5) • Reflexes: Diffusely brisk
Sensory exam	• Normal
Coordination	• Normal (accounting for spasticity and weakness)
Gait	• Impairment noted (high steppage gait with foot occasionally dragging on the ground) • Unable to stand on right toe

Motor exam flags continue to support a possible ALS diagnosis.

Differential diagnosis

Based on the patient history and neurological exam, the lesion location is identified as follows:

- Upper motor neuron involvement in cervical and lumbosacral regions (diffuse hyperreflexia)
- Lower motor involvement in the lumbosacral region (weakness and atrophy in both legs)

The progressive nature of the symptoms, upper and lower motor neuron involvement, lack of pain or sensory symptoms, and unremarkable neuroimaging indicate a possible diagnosis of ALS and call for expedited referral to an ALS clinic.

Across Canada, ALS clinics have formed the Canadian ALS Research Network (CALS), which include multidisciplinary teams for optimized care and opportunities to participate in research.

Visit the ALS Canada website to find an ALS clinic near you.

Patients can be referred to ALS clinics:

- Without a confirmed diagnosis and as soon as ALS is suspected
- Prior to the completion of diagnostic testing
  - If not already done, an MRI and a pulmonary function test (i.e., FVC test) are ordered at the time of referral

Early referral to ALS clinics may reduce diagnosis delays and may:[3]

- Improve patient outcomes
- Reduce unnecessary interventions
- Avoid adverse psychological effects of diagnostic delay
- Prevent missed opportunities to use approved therapies or participate in clinical trials

ALS, amyotrophic lateral sclerosis; FVC, forced vital capacity.

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1. Hodgkinson VL, et al. Provincial differences in the diagnosis and care of amyotrophic lateral sclerosis. *Can J Neurol Sci*. 2018;45(6):652-659. **2.** Joyce NC, et al. Electrodiagnosis in persons with amyotrophic lateral sclerosis. *Pm R.* 2013;5(5 Suppl):S89-95. **3.** Kiernan MC, et al. Amyotrophic lateral sclerosis. *Lancet.* 2011;377(9769):942-955. **4.** Hardiman O, et al. Clinical diagnosis and management of amyotrophic lateral sclerosis. *Nat Rev Neurol.* 2011;7(11):639-649. **5.** Zarei S, et al. A comprehensive review of amyotrophic lateral sclerosis. *Surg Neurol Int.* 2015;6:171. **6.** Cedarbaum JM, et al. The ALSFRS-R: A revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). *J Neurol Sci.* 1999;169(1-2):13-21. **7.** Mitchell JD, et al. Amyotrophic lateral sclerosis. *Lancet.* 2007;369(9578):2031-2041. **8.** Mayo Clinic. Amyotrophic lateral sclerosis: Symptoms and causes. Available at: https://www.mayoclinic.org/diseases-conditions/amyotrophic-lateral-sclerosis/symptoms-causes/syc-20354022. Accessed October 2, 2020. **9.** Statland JM, et al. Patterns of weakness, classification of motor neuron disease, and clinical diagnosis of sporadic amyotrophic lateral sclerosis. *Neurol Clin.* 2015;33(4):735-748. **10.** Bock M, et al. Progression and effect of cognitive-behavioral changes in patients with amyotrophic lateral sclerosis. *Neurol Clin Pract.* 2017;7(6):488-498. **11.** ALS Association. Symptoms and diagnosis. Available at: http://www.alsa.org/about-als/symptoms.html. Accessed October 2, 2020. **12.** Finegan E, et al. Pathological crying and laughing in motor neuron disease: Pathobiology, screening, intervention. *Front Neurol.* 2019;10(260). **13.** ALS Canada. A guide to ALS patient care for primary care physicians. Available at: https://als.ca/wp-content/uploads/2017/02/A-Guide-to-ALS-Patient-Care-For-Primary-Care-Physicians-English.pdf. Accessed October 2, 2020. **14.** National Institute for Health and Care Excellence. Motor neurone disease: Assessment and management. Available at: https://www.nice.org.uk/guidance/ng42/resources/motor-neurone-disease-assessment-and-management-pdf-1837449470149. Accessed October 2, 2020. **15.** Ghasemi M. Amyotrophic lateral sclerosis mimic syndromes. *Iran J Neurol.* 2016;15(2):85-91. **16.** Brooks BR, et al. El Escorial revisited: Revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord.* 2000;1(5):293-299.

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