Diagnostic Odyssey in ALS

Patient #1: Limb Onset ALS

65-year-old-woman

Case contributor and commentary:

Dr. Martina Wiedau, MD
University of California Medical Center |
Los Angelas, California

Initial Symptoms

Medical History:

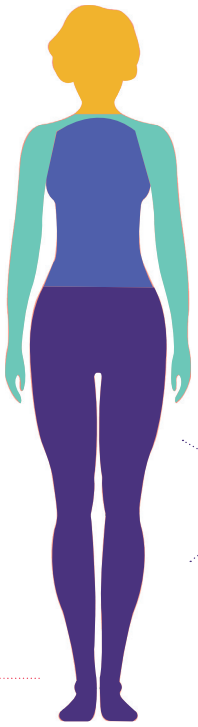
- History of hypercholesterolemia
- No family history of ALS or neurological disease

No Symptoms Affecting:

- Vision
- Speaking
- Swallowing
- Sensation
- Balance

Figure Key

- Bulbar region
- Cervical region
- Thoracic region
- Lumbar region
- Site of key/defining symptoms



Fasciculations of left arm muscles

Loss of left-hand muscles

Difficulty putting key in door and typing for past 2 months

- Left leg weakness advanced distal proximal
- Reduced walking distance to 1 block
- Noted muscle fasciculations and leg cramps for past 1 year

12-month history of left foot drop and fall

ALS Risk Factors

- Advancing age, median age at onset 55-60
- Male to female ratio: 1:2
- Family history of ALS, mostly dominant inheritance patterns
- Common genes: C9ORF72, SOD1, FUS, TDP-43

Commentary: Symptoms often start in one body site (focal onset) and then spread to the other side and to neighboring body regions.[1] In this case, as in approximately three-quarters of all focal onset ALS cases,[2] symptoms began in the limb/foot. Consideration of non-motor symptoms, such as sialorrhea/increased saliva, pseudobulbar affect/inability to control emotional expression, and fatigue, can help with diagnosis. Diagnosis is often delayed by an average of 12 months after symptom onset.[3]

In this case, the diagnosis was made 10 months after first symptom was noticed.

Supported in part by a medical education grant from Mitsubishi Tanabe Pharma America

Diagnostic Odyssey in ALS

Patient #1: Limb Onset ALS

65-year-old-woman

Case contributor and commentary:

Dr. Martina Wiedau, MD
University of California Medical Center |
Los Angelas, California

Physical Exam

Following observation of initial symptoms, a physical examination was performed:

- Cranial nerves: tongue fasciculations
- Motor: normal tone, reduced muscle bulk of left first dorsal interosseus, thenar, interossei, left calf
- Fasciculations/muscle twitches in all limbs and torso muscles
- Weakness in left first dorsal interosseus, interossei, finger extensors 3/5, left hip 4/5, left anterior dorsal flexion/toe extension 2/5,
- Deep tendon reflexes: 3+/4 with spreading bilateral upper extremities and lower extremities, (normal is 2/4 without spreading)
- Positive Babinski reflex, palmomental reflex, jaw jerk, snout. Absent superficial abdominal reflex, which is present in most healthy persons
- Gait analysis: left foot drop

Commentary: The first step in the diagnostic process is an examination by a neurologist. During the exam, the neurologist will look for typical features of ALS that may include muscle weakness, lower motor neuron (LMN) features, upper motor neuron (UMN) features, or emotional changes.[4] The neurologist may also perform tests to rule out other possible causes of the patient's symptoms.

Laboratory Tests

After the physical exam, follow-up tests were ordered:

Electromyography (EMG)/nerve conduction studies (NCS):

- Fibrillations, positive sharp waves and large polyphasic units of long duration firing at high rates with a reduced recruitment pattern
- Widespread changes in the distribution of spinal levels controlling bulbar, cervical, thoracic and lumbar regions, including clinically unaffected muscles
- Normal motor and sensory nerve conduction study results

Blood work :

- Creatine kinase: 265, normal
- Negative genetic ALS panel

Imaging:

- Normal brain & C-spine MRI

Supported in part by a medical education grant from Mitsubishi Tanabe Pharma America

Diagnostic Odyssey in ALS

Patient #1: Limb Onset ALS

65-year-old-woman

Case contributor and commentary:

Dr. Martina Wiedau, MD
University of California Medical Center |
Los Angelas, California

Commentary: The second step in the diagnostic process often involves laboratory testing, including: (1) electromyography (EMG), which tests nerve conduction and electrical activity in selected muscles, (2) magnetic resonance imaging (MRI) of the neck, head and/or lower spine, and (3) a series of blood tests.[5] In some cases, urine tests, genetic tests, or a lumbar puncture (also called a spinal tap) may be necessary. Findings from these tests can help with diagnosis. In ALS, nerve conduction measured by EMG is typically normal, distinguishing the disease from another condition that presents similarly, multifocal motor neuropathy. Electrical activity measured by EMG, however, often identifies lower motor neuron abnormalities in ALS. EMG test results can be helpful when ALS is suspected, but clinical criteria for definite diagnosis are not fulfilled.

Diagnosis

Differential Diagnosis:

Progressive weakness of limbs, atrophy and fasciculations with hyperreflexia and sparing of bulbar muscles resulted in consideration of the following differential diagnoses:

- C-spine disease/myelopathy
- Combination of brain disease such as vascular disease and neuromuscular disorder, such as radiculopathies or myasthenia gravis

Criteria Used for Diagnosis:

- UMN features in cervical and lumbar region
- LMN features in bulbar, cervical, thoracis and lumbar regions

Diagnosis:

ALS per Airlie House and Awaji criteria

Commentary: The revised El Escorial criteria and Awaji criteria are the most commonly used diagnostic criteria for ALS. Consensus diagnostic classifications based on these two criteria are available.[6]

Clinically definite ALS: Clinical evidence of simultaneous LMN and UMN signs in at least 3 of 4 nervous system regions (bulbar, cervical, thoracic, lumbar). LMN signs can be obtained by clinical exam or EMG.

Clinically probable ALS: Clinical evidence of simultaneous LMN and UMN signs in 2 of 4 nervous system regions (bulbar, cervical, thoracic, lumbar). LMN signs can be obtained by clinical exam or EMG.

Clinically possible ALS: Clinical evidence of simultaneous LMN and UMN signs in 1 of 4 nervous system regions (bulbar, cervical, thoracic, lumbar). LMN signs can be obtained by clinical exam or EMG. UMN signs found alone in > 2 regions or LMN signs found rostral to UMN signs.

Supported in part by a medical education grant from Mitsubishi Tanabe Pharma America

Diagnostic Odyssey in ALS

Patient #1: Limb Onset ALS

65-year-old-woman

Case contributor and commentary:

Dr. Martina Wiedau, MD
University of California Medical Center |
Los Angelas, California

Disease Progression

The diagnosis was made 10 months after the initial weakness was noticed. The patient experienced the following course of disease, passing away from respiratory failure at 44 months after symptom onset:

Diagnosis at 10 months following symptom onset

Symptom onset	15 mos	20 mos	24 mos	32 mos	34 mos	44 mos
Progressive weakness of arms and legs						
	Started using cane					
		Started using walker				
			Developed bulbar symptoms			
				Developed respiratory symptoms		
				Started using wheelchair		
					Started using BiPap	
						Passed away from respiratory failure

Commentary: The typical survival of individuals with ALS is three to five years following diagnosis. ~30% of ALS patients are alive five years after diagnosis, and 10-20% survive for more than 10 years. Respiratory failure is the most common cause of death from ALS.[7] Factors associated with more favorable survival include: younger age at symptom onset, male gender, and limb rather than bulbar symptom onset.[8] Survival beyond 20 years is rare, but possible, and is in part dependent upon treatment decisions made by patients and their families (e.g. nutritional support, feeding tube, etc.).

References

1. Ravits JM, la Spada AR. ALS motor phenotype heterogeneity, focality, and spread: Deconstructing motor neuron degeneration. Neurology. 2009;73(10):805-811. doi:10.1212/WNL.0b013e3181b6bbbd
2. Turner MR, Brockington A, Scaber J, et al. Pattern of spread and prognosis in lower limb-onset ALS. Amyotrophic Lateral Sclerosis. 2010;11(4):369-373. doi:10.3109/17482960903420140
3. Brooks BR. Diagnostic dilemmas in amyotrophic lateral sclerosis. In: Journal of the Neurological Sciences. Vol 165. J Neurol Sci; 1999. doi:10.1016/S0022-510X(99)00019-2
4. Louis ED, Mayer SA, Noble JM. Merritt's Neurology. 14th ed. Wolters Kluwer; 2021.
5. Oskarsson B, Gendron TF, Staff NP. Amyotrophic Lateral Sclerosis: An Update for 2018. Mayo Clinic Proceedings. 2018;93(11):1617-1628. doi:10.1016/j.mayocp.2018.04.007
6. Costa J, Swash M, de Carvalho M. Awaji criteria for the diagnosis of amyotrophic lateral sclerosis: A systematic review. Archives of Neurology. 2012;69(11):1410-1416. doi:10.1001/ARCHNEUROL.2012.254
7. O H. Management of respiratory symptoms in ALS. Journal of neurology. 2011;258(3):359-365. doi:10.1007/S00415-010-5830-Y
8. Chiò A, Logroscino G, Hardiman O, et al. Prognostic factors in ALS: A critical review. Amyotrophic Lateral Sclerosis. 2009;10(5-6):310-323. doi:10.3109/17482960802566824

Supported in part by a medical education grant from Mitsubishi Tanabe Pharma America