



# Bulbar Dysfunction in Amyotrophic Lateral Sclerosis: A Case Report of a Rare Neurodegenerative Condition and Literature Review

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## Abstract

Amyotrophic Lateral Sclerosis is a debilitating disorder characterized by degeneration of upper and lower motor neurons. Approximately 90% of all ALS cases are found to occur sporadically, whereas 10% of them are familial. ALS can characteristically present as bulbar dysfunction. We report the case of an 81-year-old female who presented with worsening dysarthria, dysphagia, and weight loss of one-year duration. She was later diagnosed with clinically possible to probable ALS based both on results of her laboratory tests and the diagnosis classification of Awaji-Shima Consensus Recommendations and the revised El Escorial Criteria. Riluzole and Edavarone are currently the only two drugs approved by the United States Food and Drug Administration (FDA) for ALS treatment. These drugs work mainly by delaying the course of the disease. Given the scant amount of treatment options available, further studies are warranted to better comprehend the pathogenesis of ALS and find novel and more efficacious ways of addressing it.

**Keywords:** Amyotrophic Lateral Sclerosis; Bulbar Dysfunction; Pathogenesis; Treatment

## Abbreviations

ALS: Amyotrophic Lateral Sclerosis; FDA: Food and Drug Administration; EMG: Electromyography; MRI: Magnetic Resonance Imaging; EGD: Esophagogastroduodenoscopy; PEG: Percutaneous Endoscopy Gastrotomy; LMN: Lower Motor Neuron; UMN: Upper Motor Neuron; WFN: World Federation of Neurology; EAATs: Excitatory Amino Acid Transporters; SOD1: Superoxide Dismutase 1; ATP: Adenosine Triphosphate

## Introduction

Also known as Lou Gehrig disease, Amyotrophic Lateral Sclerosis is a rapidly progressive neurodegenerative disorder caused by pathologic inclusions inside the upper and lower motor neurons. The upper motor neuron signs of the disease include slowness, hyperreflexia and spasticity, whereas the lower motor neuron findings include weakness, atrophy, or amyotrophy. Two different types of criteria can be used for the diagnosis of ALS.

These are the Awaji criteria and the El Escorial criteria. Because of the broad clinical features of ALS, scientists, researchers and clinicians around the world have set forth a commonly agreed upon consensus document to facilitate its diagnosis at El Escorial, Spain on May 29-31, 1990. The consensus criteria were submitted to and subsequently accepted by the Executive Committee of the World Federation of Neurology (WFN) Research Group on Neuromuscular Diseases. Costa et al. showed that using the Awaji criteria results in better clinical outcomes in that they allow earlier diagnosis and clinical trial entry in ALS than the previously accepted gold standard, the El Escorial criteria [1].

Bulbar dysfunction is one of the many atypical presentations of ALS, which can make its early identification challenging when considering possible differential diagnosis. It is however the responsibility of the physician to make the correct diagnosis of ALS at its early stage in order to be able to outline the appropriate plan of care. We describe the case of an 81-year-old patient who presented with worsening dysarthria, dysphagia, facial weakness, throat pain, and weight loss of one-year duration. This study discusses the Awaji and El Escorial criteria for the diagnosis of ALS, the diagnostic classification of ALS, the diagnostic workup leading to the clinical diagnosis of ALS, the importance of electromyography (EMG) studies in further corroborating the diagnosis, the approved drugs that are available to delay the course of the disease, and finally the pharmacological research projects that are currently underway to better address the condition.

## Case Presentation

An 81-year-old female with past medical history of breast cancer status post lumpectomy and chemoradiation, gastroesophageal reflux disease, coronary artery disease with stent placement, osteoarthritis, osteoporosis, and depression

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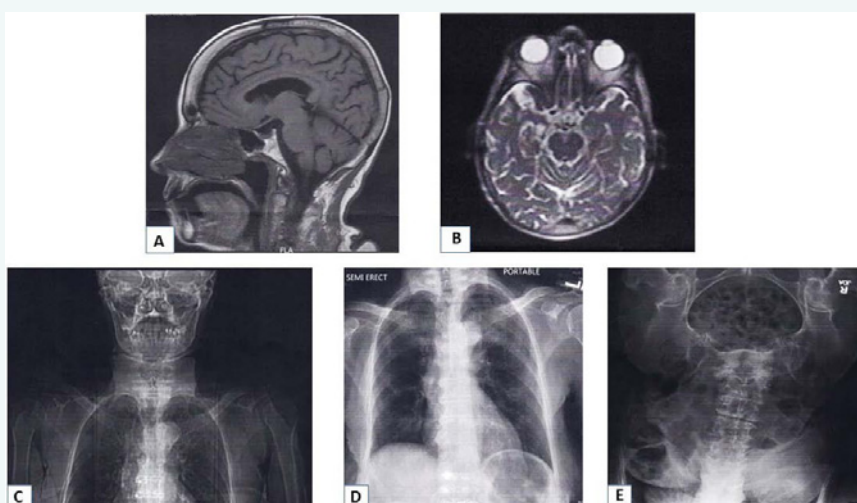
presented to the hospital with dysphagia and throat discomfort after eating spicy food. She was in her normal state of health one year ago, when she first noticed sudden onset of slurring of her speech and mild inability to easily swallow both solid and liquid foods. This has quickly progressed over the course of six months to complete inability to speak and excessive drooling of food and saliva from her mouth as she makes an effort to ingest only part of her meal. She has noticed progressively worsening oropharyngeal dysphagia, dysarthria and weight loss over the course of the past year. According to her primary care physician, she previously presented to another facility at the very onset of her symptoms one year ago, but Computed Tomography and Magnetic Resonance Imaging of the brain were normal. She was then advised to obtain gastrotomy and Neurology evaluation for diagnosis of suspected bulbar ALS and was subsequently discharged home. Patient was reluctant about undergoing Percutaneous Endoscopic Gastrotomy (PEG) and did not follow up. She is aphasic, but is alert and oriented to person, place and time. She is able to communicate by writing on a sheet of paper. On physical examination, she is lying in bed and appears lethargic and cachectic. Examination of upper and lower extremities reveals 4/5 strength bilaterally as well as facial weakness. Her home medications include calcium carbonate, cyproheptadine, paroxetine, aspirin, ferrous sulphate, Atorvastatin, Ranitidine and Ensure. She denies smoking, drinking alcohol and use of illicit drugs.

Patient was subsequently admitted and underwent investigations. On the list of differential diagnosis were stroke, paraneoplastic syndromes, different autoimmune diseases and infectious diseases. A repeat Magnetic Resonance Imaging (MRI) at present visit also resulted in normal findings without evidence of acute infarction, intracranial bleeding or mass effect (Figures 1A and 1B). No interval changes have occurred since her first MRI. MRI of the cervical spine displayed narrowing of the subarachnoid space of the cervical region without focal canal stenosis, cord displacement or cord compression. Computed Tomography

of the neck soft tissue without contrast did not indicate any foreign bodies (Figure 1C). X-Ray of the chest shows diffuse increased interstitial markings without atelectasis or pneumonia (Figure 1D). It also demonstrated atherosclerotic aorta. X-Ray of the abdomen did not reveal any evidence of obstruction or cholelithiasis (Figure 1E). X-Ray of the skull was unremarkable. Patient also underwent esophagogastroduodenoscopy (EGD) which effectively ruled out achalasia. It further denoted extrinsic compression of mid esophagus related to anatomical compression from aorta. Inflammation was found in the stomach as well. Biopsy of the proximal and distal esophagus ruled out eosinophilic esophagitis. Laryngoscopy exhibited inability to elicit movement of vocal cords on command. There were no masses or lesions found.

Different serologic tests were carried out to narrow down the possible differential diagnosis. Among these, a Rapid Plasma Reagin test effectively ruled out syphilis. Antibodies to Jo-1 were negative, eliminating dermatomyositis. Lyme disease IgG and IgM were negative. Negative antinuclear antibodies effectively excluded conditions such as Systemic Lupus Erythematosus and Systemic Sclerosis. Antibodies to Ro and La were negative as well, dismissing Sjogren Syndrome. Myasthenia Gravis was also excluded with negative acetylcholine receptor antibodies and negative musk antibody test. Furthermore, hemoglobin electrophoresis did not display any hemoglobin variant. Thyroid function tests demonstrate abnormally elevated serum Thyroid Stimulating Hormone. Results of complete blood count and basic metabolic panel were unremarkable.

Due to weight loss and malnutrition, patient agreed for and underwent percutaneous endoscopic gastrotomy. In sight of the progressive pattern of her worsening bulbar dysfunction and facial weakness, she was clinically diagnosed with possible to probable bulbar ALS based on the classification of Awaji-Shima Consensus recommendations and the revised El Escorial Criteria. She was prescribed Omeprazole to prevent gastroesophageal



**Figure 1** Sagittal (A) and axial (B) MRI of the brain demonstrating normal, age-appropriate findings. (C) Computed Tomography Neck and soft tissue without contrast. (D) Chest X-Ray Anteroposterior view. (E) X-Ray of the abdomen supine anteroposterior view..



reflux disease. She was also referred for electromyography evaluation at another facility to further support this diagnosis and initiate the appropriate care at the specialized ALS center available at that facility.

## Discussion

This case is unique in that it features a pure motor bulbar-onset ALS, a rare variant present in only 30% of all ALS patients. This variant is also associated with a poor prognosis, and its diagnosis is complicated by the fact that its clinical features mimic other diseases. It is however of the utmost importance to make the right clinical diagnosis of bulbar ALS early in order to be able to delay its course, enable patients to have enough time for end of life planning while they still have capacity, and to provide the adequate palliative care support and treatment that these patients deserve.

Mazon et al., stated that the revised criteria of the WFN Research Group on Motor Neuron Diseases recommends conventional imaging in “clinically probable” or “possible ALS” while imaging is not required in “clinically definite” disease [2]. There is not a pre-defined set of tests that a clinician must carry out to diagnose ALS, but one can arrive to this diagnosis by first ruling out other mimickers of the disease such as paraneoplastic syndromes and autoimmune diseases. This explains the use of diagnostic imaging and serologic tests in this study. Once this is done, the clinician can rely on either clinical or electrophysiological evidences as defined by the Awaji-Shima consensus recommendations and the revised El Escorial Criteria to make the diagnosis of the disease. Table 1 from Costa et al., summarizes the difference between the two diagnostic criteria, as well as the diagnostic classification [1].

The patient in this study was diagnosed as having clinically probable to possible bulbar ALS. She primarily has upper and lower motor neuron lesions resulting in both dysarthria and dysphagia. Laryngoscopy demonstrated inability to move vocal cord muscles on command. Furthermore, physical examination reveals weakness of her facial muscles. Having clinical signs of UMN and LMN in the bulbar region and weakness of facial muscles meet the requirements for clinically probable to possible ALS established by the Awaji-Shima consensus recommendations and the revised El Escorial criteria. Patient was referred for electromyography to further support this diagnosis with

electrophysiological evidences and to ALS center for initiation of treatment.

As asserted by Joyce et al., electrophysiological evidence is now considered equivalent to clinical signs and symptoms in reaching diagnostic certainty of ALS [3]. Electrodiagnostic studies include peripheral nerve conduction studies and electromyography. Moreover, as recommended by the Awaji-Shima consensus group, the recent changes in the revised El Escorial criteria have increased the diagnostic significance of fasciculation potentials to equal that of fibrillation and positive sharp wave potentials in the needle EMG examination of the patient suspected of having ALS [3]. EMG that is consistent with ALS typically demonstrates widespread acute and chronic muscular denervation and reinnervation.

According to Elman et al., the neuropathology of the Amyotrophic Lateral Sclerosis is marked by the presence of cytosolic inclusions inside the upper and lower motor neurons and glia, which notably stain positive for ubiquitin, TAR DNA-binding protein (TDP-43), fused in sarcoma FUS protein or optineurin [4]. There is sclerosis of the lateral columns of the spinal cord and loss of anterior horn cells. Meininger et al. however reports that the oculomotor, trochlear and abducens nuclei which control eye movements and the Onufrowicz's nuclei which control fecal and urinary continence are generally intact [5]. There are two main presentations of ALS at disease onset: spinal-onset ALS and bulbar-onset ALS. Shellikeri et al., reports that spinal-onset ALS occurs in 70% of ALS patients and presents with muscle weakness and atrophy in limbs and trunk whereas the remaining 30% of ALS patients with bulbar-onset present with impaired speech and swallowing musculature as in this patient. Approximately 85% of spinal-onset ALS however displays bulbar changes with disease progression [6]. Bulbar-onset ALS is the most debilitating as it was found to be associated with fastest decline, less than 2 years survival rate post diagnosis and a significantly reduced quality of life [6].

Furthermore, the diagnosis of bulbar-onset ALS is also frequently missed. Chen et al., reports a retrospective study that was completed to determine the incidence of voice disturbance as the presenting sign of Amyotrophic Lateral Sclerosis. The study has reviewed records of patients presenting with voice disturbance at a voice center and ALS patients at a neurology clinic from January 1998 to March 2003. The results of the study

**Table 1:** Summary of Revised El Escorial Criteria and Awaji Criteria for ALS Diagnosis: Differences Between Awaji-Shima Consensus Recommendations and the Revised El Escorial Criteria. Data collected from Costa et al. [1].

Criteria	Clinically definite ALS	Clinically probable ALS	Clinically possible ALS
<b>Revised El Escorial criteria</b>	UMN and LMN deficits in three regions of the body.	UMN and LMN deficits in a minimum of two regions of the body. Some of the UMN deficits should be located rostrally to the LMN deficits.	UMN and LMN deficits in one region only or UMN deficits in two or more regions, or LMN deficits located rostrally to UMN signs
<b>Awaji-Shima criteria</b>	Clinical or electrophysiological proof of UMN and LMN deficits in a minimum of two spinal regions and the bulbar region, or UMN and LMN deficits in three spinal regions	Clinical or electrophysiological proof of UMN and LMN deficits in a minimum of two regions of the body. Some of the UMN deficits should be located rostrally to the LMN deficits.	Clinical or electrophysiological evidence of UMN and LMN deficits only in two or more regions of the body, or LMN deficits located rostrally to UMN deficits.

**Abbreviations:** UMN: Upper Motor Neurons, LMN: Lower Motor Neurons, ALS: Amyotrophic Lateral Sclerosis



concluded that 15 of 1759 patients with voice disturbance were later diagnosed with ALS. In addition, the study showed that of the 220 ALS patients presenting to neurology clinic, 44 had bulbar symptoms and 19 had initially presented to an otolaryngologist. Dysarthria, dysphagia, tongue fasciculation, and incomplete vocal fold closure were common findings. Moreover, the study also demonstrated that neuromuscular disease was missed in 8 of 19 ALS patients seen by an otolaryngologist [7].

Approximately 90% of ALS cases are sporadic whereas 5 to 10% of them are familial. In effect, as reported by Zarei et al., epidemiologic studies have revealed that multiple environmental factors are thought to contribute to sporadic cases [8]. Among these are smoking which increases inflammation, oxidative stress and neurotoxicity caused by heavy metals contained in cigarette smoke. In addition, prolonged exposure to chemicals such as pesticides, fertilizers, insecticides, herbicides, formaldehydes, and lead has been associated with increased risk of ALS. Oxidative damages caused by radiation and electromagnetic fields have also been linked to ALS pathogenesis. Finally, diets containing elevated amount of glutamate (tomatoes, mushrooms, milk, and cheese) have been linked with adverse effects in ALS patients. This is due to the fact that elevated glutamate receptor stimulation results in increased intracellular calcium levels which cause selective neuron death similar to ALS mechanism. On the other end, Omega 3 with Vitamin E has been reported to reduce ALS risks up to 60% due to their anti-inflammatory properties [8]. Zarei et al., also reports reduced astroglial excitatory amino acid transporters 2 (EAAT2) in the motor cortex and spinal cord of ALS patients [8]. In normal physiology, glutamate is made in the pre-synaptic space and released into synaptic cleft where it stimulates post synaptic receptors, causes calcium influx and firing of motor neurons. It is then removed from the synaptic cleft by EAATs which help maintain concentration gradient balance and avoid excitotoxic neuronal damage. ALS patients have reduced EAATs, which leads to increased extracellular glutamate, overstimulation of glutamate receptors, excitotoxic neural degeneration, excessive calcium influx, excessive motor neurons firing, and destructive biochemical processes within the cell [8]. In addition, patients with familial ALS are found to have mutation in the gene encoding for the enzyme copper-zinc superoxide dismutase 1 (SOD1). This results in a misfolded protein which deposits in the outer membrane and matrix of spinal cord mitochondria. This causes mitochondrial dysfunction with impaired ATP production, calcium homeostasis, axonal transport of mitochondria, and apoptotic triggering [8].

There are to this date two drugs approved by the United States FDA for use in ALS. Riluzole which was approved in 1995 and Edavarone which was approved in 2017. Dharmadasa et al., states that Riluzole was found to be associated with a short survival benefit of 2 to 3 months, which is equivalent to a 9% increase in 1-year survival [9]. Moreover, Fang et al., reports that results from the original dose-ranging trial comprising 959 patients who were randomly assigned to Riluzole (50 mg/day, 100mg/day, or 200 mg/day) or placebo demonstrated that 100 mg/day of Riluzole is associated with longer survival in the latest stage of ALS before death (stage 4) compared to placebo (hazard ratio 0.55, 95% CI 0.36-0.83, log-rank  $p=0.037$ ) [10]. Interestingly, it was also noted

that the time from stages 2 or 3 to subsequent stages or death did not differ between Riluzole treatment groups and placebo [10]. Furthermore, Cruz et al., explains that Edavarone's therapeutic effect is linked to its antioxidant and neuroprotective effects and its role in prevention of oxidative stress [11]. Edavarone also works by delaying disease progression.

## Conclusion

In the United States, Mehta et al., reported an ALS prevalence of 5.2 per 100 000 in 2015 based on the data from the United States National ALS Registry [12]. There is currently not a definitive cure for ALS, but several clinical trials are currently underway to find a more efficacious treatment for the disease. Raising awareness about this rare neurological condition and having a better understanding of the various clinical features and pathogenesis of ALS constitute some of the most prominent steps toward the resolution of this puzzling condition.

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