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A Rare Case of Juvenile Amyotrophic Lateral Sclerosis

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ABSTRACT

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disorder affecting both upper and lower motor neurons. The term Juvenile ALS (JALS) is used for patients with symptoms onset before the age of 25. This report is written to discuss the clinical presentation of JALS, a highly rare form of motor neuron disease. We report a 25-year-old male patient with JALS who presented to the neurology clinic with complaints of progressive weakness in the upper and lower extremities since the age of 21. The patient also experienced speech disturbance. There was no family history found. Neurological examination revealed mixed upper and lower motor neuron weakness and muscle atrophy in the upper and lower extremities, as well as dysarthria with tongue muscle atrophy. Magnetic Resonance Imaging of the spinal cord with contrast did not show significant findings. Nerve conduction study found axonal lesions in motor neurons and normal sensory neurons. Electromyography showed signs of active and chronic denervation of the masseter muscle, thoracic paravertebral muscles, and muscles of the upper and lower extremities. This patient met the criteria for clinically definite ALS according to the revised El Escorial criteria. Approximately 5% of ALS cases are estimated to occur in individuals under the age of 30. Most JALS cases are familial, but some occur sporadically without a family history. The prognosis of the disease varies from rapidly progressive to slow progression. The diagnosis of JALS is based on the development of a clinical syndrome that meets the diagnostic criteria for ALS with onset before the age of 25. JALS is a diagnosis to be considered in young adults with combined clinical manifestations of upper and lower motor neuron dysfunction with bulbar palsy, although it is a rare disease.

Keywords: clinical manifestations, diagnosis, juvenile amyotrophic lateral sclerosis

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a heterogeneous neurodegenerative syndrome involving both motor and extra-motor systems, characterized by multiple pathophysiological mechanisms and diverse clinical and genetic subphenotypes. ALS is marked by progressive weakness of skeletal muscles resulting from the destruction of neurons with characteristic upper and lower motor neuron weakness. While ALS is the most common motor neuron disease, it remains a rare condition. The global incidence of ALS ranges from 2-3 per 100,000, with a prevalence of 4-5 per 100,000. Classic ALS most commonly occurs in the fifth to sixth decades of life, but several studies have identified cases of ALS in children, adolescents, and young adults.[1,2] ALS with symptom onset before

the age of 25 is termed juvenile ALS (JALS). JALS is an extremely rare form of ALS, which can occur sporadically or be familial.[3] JALS may present with varied clinical manifestations and courses different from classic ALS.[4] There are currently no specific guidelines for the diagnosis and management of JALS. This report is written to discuss the characteristics of JALS, an exceedingly rare form of motor neuron disease.

CASE REPORT

A 25-year-old Balinese male patient was referred to the neurology outpatient clinic with complaints of weakness in all four limbs, which he had been experiencing for approximately 4 years. Initially, weakness was felt in the right hand, then spread to the left hand, and both legs. Initially, the patient was still able to carry out daily activities, but since 2019, he has had difficulty performing daily activities. For the past 2 years, the patient has been unable to perform activities independently and tends to stay in bed. Since the beginning of 2022, the complaints have worsened, prompting the patient to seek treatment from doctors at the hospital. Complaints of limb weakness were also accompanied by slurred speech since 1 year ago. The speech difficulty had also been increasingly severe. Other complaints such as tingling or numbness, crooked lips, headache, neck pain, and urinary and bowel disturbances were denied. There was no history of previous illness or trauma. There was no family history of similar complaints.

On physical examination, the patient was alert and oriented with vital signs within normal limits. Neurological examination revealed tetraparesis with grade 3 in the upper extremities and grade 4 in the lower extremities based on MRC grading. Increased tone and hyperreflexia were found in the lower extremities. Bilateral positive Babinski reflex and clonus were observed. Atrophy was found in the bilateral abductor pollicis brevis muscles and bilateral first dorsal interossei muscles (Figure 1).

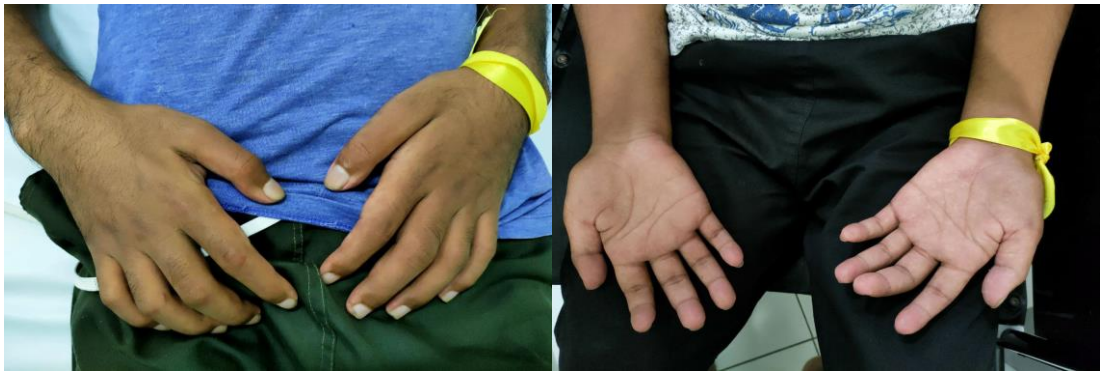

Figure 1. Signs of atrophy in the muscles of the hands

Examination of the cranial nerves revealed dysarthria and atrophy of the intrinsic muscles of the tongue (Figure 2). Sensory examination and autonomic function were within normal limits.

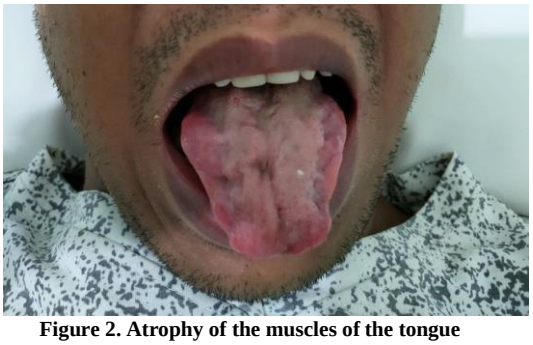

Figure 2. Atrophy of the muscles of the tongue

The nerve conduction study (NCS) was conducted on this patient and revealed decreased amplitude of the median and ulnar nerves (Table 1).

Table 1. NCS result

	Latency (ms)	Amplitude (M – mV/ S - µV)	Nerve conduction velocity (m/s)
Motoric nerve			
Median	-	-	-
Ulnar	3.77	0.94	58.4
Peroneus	7.8	3.0	120
Tibial	6.48	7.4	45.5
Sensoric nerve			
Median	3.08	21.6	57.6
Ulnar	2.55	45.6	56.9
Sural	3.14	13.7	52.9

The electromyography (EMG) examination revealed signs of chronic denervation and neurogenic motor unit action potentials (MUAP) in the right masseter muscle, right flexor carpi radialis muscle, right biceps muscle, right thoracic paravertebral muscle at the level of T10, right lateral head of the gastrocnemius muscle, and right tibialis anterior muscle (Figure 3).

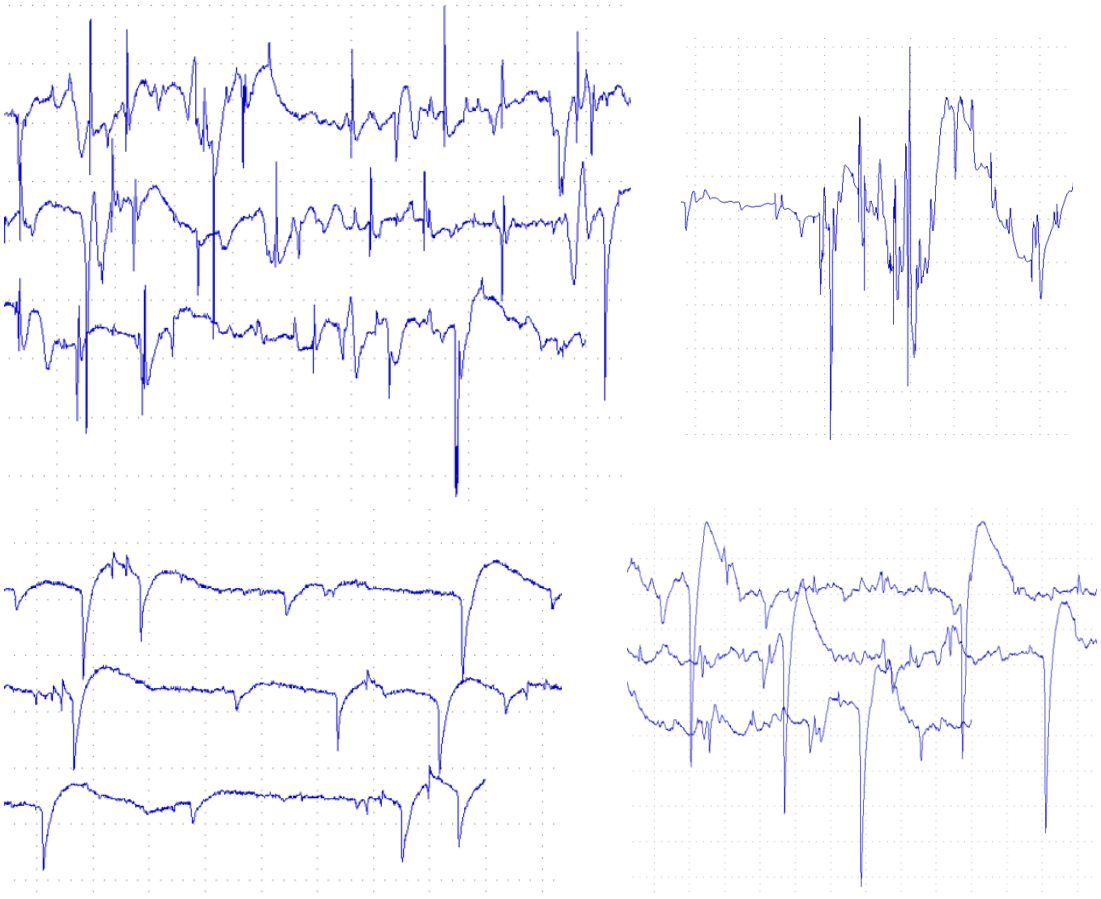

Figure 3. EMG results

The Magnetic Resonance Imaging (MRI) examination with contrast of the cervical area did not reveal any significant structural abnormalities (Figure 4). The patient is currently undergoing rehabilitation therapy.

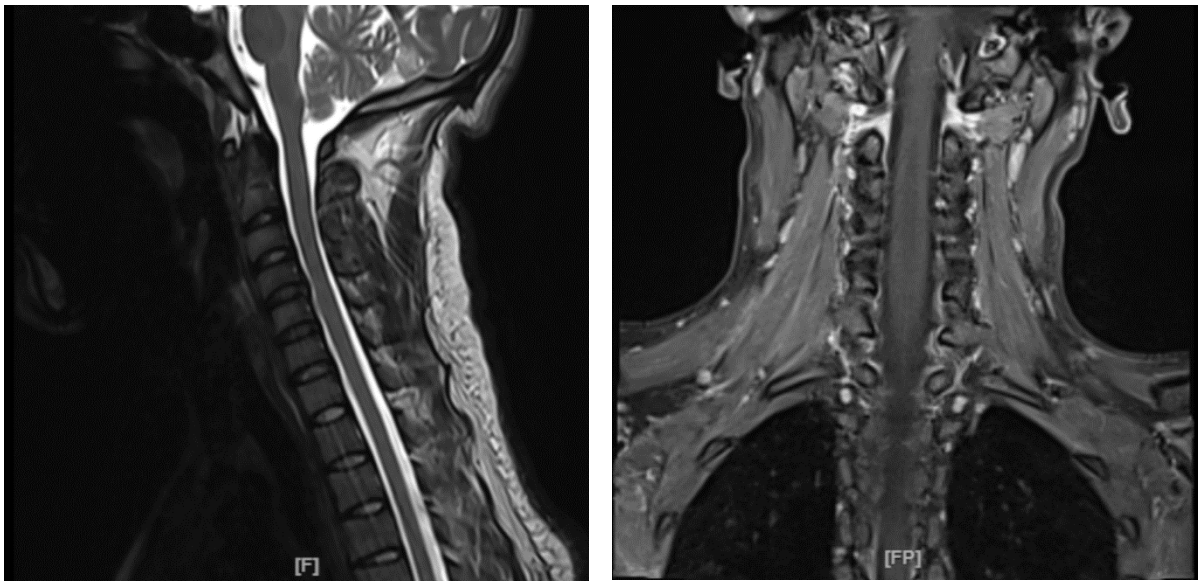

Figure 4. Cervical MRI results

DISCUSSION

Juvenile ALS, a form of ALS that occurs with onset before the age of 25, is one of the rare motor neuron disorders characterized by degeneration of both UMN and LMN. The exact prevalence and incidence of JALS are not yet known. A cohort study in Tunisia reported JALS occurring in about 5.71% of patients. Researchers in this study reported exposure to environmental factors influencing the occurrence of ALS at a younger age in Tunisia. These environmental factors include exposure to heavy metals, chemical fluids, electromagnetic radiation, living in rural areas, pesticide use, and cigarette smoke.[5] The average age of JALS onset is reported to range between 16-21 years.[5,6]

Juvenile ALS has several unique characteristics compared to adult-onset ALS (AO-ALS). Approximately 90% of AO-ALS cases are reported to occur sporadically. JALS is more often familial, although sporadic cases can also occur.[3,6] Sporadic JALS is characterized by a predominant male gender and longer survival time.[6] JALS is more influenced by genetic factors, with 40% of cases associated with genetic mutations, while only about 10% of AO-ALS cases are associated with genetic mutations. JALS can be inherited in an autosomal dominant or recessive pattern. The Fused in Sarcoma (FUS) gene mutation is the most commonly associated mutation with JALS. The FUS gene is involved in cell proliferation, DNA repair, transcriptional regulation, RNA transport, and microRNA formation. Other genes frequently reported in JALS cases include senataxin and ALS2. The C9orf72 gene mutation, commonly inherited in AO-ALS, is not reported to occur in JALS. The type of gene mutation plays a role in influencing the age of onset, clinical manifestations, and prognosis in JALS.[3,4] The patient in this case is male with an onset age of 21 years and is a sporadic case with no family history. However, the contribution of gene mutations in this patient cannot be evaluated due to facility limitations.

The exact mechanism of ALS is still unknown, but many pathophysiological theories of ALS have been studied. ALS pathophysiological mechanisms include oxidative stress, RNA metabolism disorders, mitochondrial dysfunction, nucleocytoplasmic transport disorders, protein aggregation, cytoskeletal disruption, glutamate and neuronal cytotoxicity, changes in regulatory gene expression, inflammation, and cell apoptosis. With FUS mutation being the most commonly found genetic abnormality, dysregulation of DNA

and RNA RNA is likely the key pathomechanism of JALS.[7,8]

To date, ALS remains a clinical diagnosis without specific biomarkers. ALS diagnosis is based on a thorough medical history, physical examination, electrophysiological findings, and exclusion of other potential causes. The most commonly used diagnostic criteria are the revised El Escorial and Awaji-Shima criteria.[9] Damage to the motor neuron system results in loss of voluntary muscle function that can occur in the extremities, bulbar region, and/or respiratory muscles, with specific symptoms depending on the affected motor pathway.[10]

The characteristic signs of ALS include a combination of progressive UMN and LMN weakness that does not involve the sensory or autonomic systems. Classic ALS can be divided into 2 types based on the initial symptoms, namely spinal onset (70%) and bulbar onset (30%). Spinal onset is reported to occur more frequently in JALS. Bulbar onset is characterized by progressive dysarthria followed by complaints of dysphagia. The presence of a combination of spastic and flaccid dysarthria is indicative of ALS. Although motor abnormalities are the main manifestation of ALS, up to 50% of patients report non-motor symptoms such as cognitive dysfunction. Physical examination reveals a combination of UMN and LMN signs in ALS patients.[1,9] The patient in this case experienced progressive limb weakness since the age of 21 years. Neurological examination found mixed upper and lower motor neuron weakness and atrophy of the upper and lower limb muscles, as well as dysarthria with tongue muscle atrophy consistent with the typical presentation of ALS.

Nerve conduction study (NCS) and electromyography (EMG) are essential diagnostic tools. The characteristic findings from NCS include normal sensory responses with normal or decreased motor component amplitudes. Electromyography is the most important electrodiagnostic modality for ALS. Signs of active denervation (fibrillation potentials and positive sharp waves) and chronic denervation in multiple myotomes are typically found on EMG.[10,11] In this case, there was a decrease in motor neuron amplitude and signs of active and chronic denervation in muscles such as the masseter, thoracic paravertebral, and muscles of the upper and lower extremities. Based on clinical and electrophysiological examinations, this case meets the definitive criteria for ALS according to the revised El Escorial criteria, which require clinical evidence or EMG signs of both upper and lower motor neuron involvement in ≥3 regions (bulbar, cervical, thoracic, and lumbosacral).

Guidelines recommend MRI of the neuroaxis extending rostrally from the lowest level of UMN signs. The majority of MRI findings in the spinal cord of ALS cases are normal, although nonspecific findings such as hyperintensity of the corticospinal tracts on T2-weighted images may be present.[1,12] In this case, cervical MRI did not reveal abnormal signals in the spinal cord. Spinal MRI in ALS is performed to rule out structural causes, inflammation, or other malignancies that may mimic the clinical presentation of combined UMN and LMN involvement resembling ALS. Differential diagnoses (DD) to consider include myopathy, post-polio syndrome, motor-predominant Charcot-Marie-Tooth disease, polyradiculopathy, neuromuscular junction disorders, Guillain-Barre syndrome, and chronic inflammatory demyelinating polyradiculoneuropathy if predominantly LMN signs are present. Nutritional myeloneuropathy, hereditary spastic paraplegia, human immunodeficiency virus myelopathy, and multiple sclerosis should be considered as DD if predominantly UMN signs are present. Cervical radiculomyelopathy is a DD if a combination of LMN and UMN signs is present.[10]

The prognosis and course of JALS vary depending on genetic mutations, ranging from very progressive to mild.[4] Respiratory insufficiency is caused by dysfunction of the

LMN of the diaphragm and accessory respiratory muscles, leading to dyspnea, orthopnea, sleep-disordered breathing, and paradoxical breathing. The onset of respiratory failure leading to mortality typically occurs 3-4 years after onset.[11]

CONCLUSION

JALS should be considered in young adults with combined clinical manifestations of upper and lower motor neuron dysfunction with bulbar palsy, despite being a rare disease. Differential diagnoses should be excluded with ancillary tests such as MRI, NCS, EMG, and other laboratory markers according to clinical findings. The revised El Escorial criteria are used to establish the diagnosis of JALS.

Declaration by Authors

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