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Case Report

Physical Medicine and Rehabilitation Section

Regional Hyperhidrosis as an Unusual Presentation of Juvenile Amyotrophic Lateral Sclerosis: A Case Report

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ABSTRACT

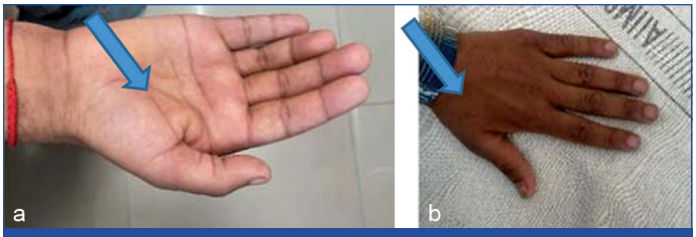
Juvenile Amyotrophic Lateral Sclerosis (JALS) is a progressive neurodegenerative disorder affecting motor neurons in the brain and spinal cord, which occurs before the age of 25 years. A 21-year-old man without a family history of neurological diseases started having increased sweating in his right hand and slippage of a pen 5 and a half years back. Within two years of the symptoms first appearing, progressive weakness in the right hand and forearm muscles, leading to difficulty in writing, grasping and lifting heavy objects, was noticed. This weakness gradually progressed to the left upper limb also. There was no history of dysphagia or dysarthria. Physical examination revealed spasticity and exaggerated deep tendon reflexes in all four limbs, along with wasting and fasciculations, with normal cranial nerves, sensory and cerebellar examinations. Blood investigations were normal. Needle Electromyography (EMG) denervation changes were noted in the upper and lower limbs and thoracic paravertebral muscles. He was diagnosed with JALS according to the modified El-Escorial criteria and age of the patient. After counselling, Riluzole was started along with non-pharmacological management. The purpose of this case is to highlight an unusual initial autonomic presentation of JALS. Here, the patient initially had increased sweating, i.e., hyperhidrosis, as the only complaint. The reason might be the increased autonomous neural firing rate.

Keywords: Adaptive devices, Autonomic dysfunction, El Escorial criteria, Riluzole

CASE REPORT

A 21-year-old male, right-handed student, presented with increased sweating in the hand for five and a half years and progressive weakness and wasting of the upper limbs for three and a half years. He was apparently healthy till five and a half years back, when he started having increased sweating of his right hand and slippage of the pen. He consulted multiple health professionals but was only counselled and not evaluated. Within two years of the symptoms first appearing, progressive weakness in the right hand and forearm muscles, leading to difficulty in writing, grasping and lifting heavy objects, was noticed, which progressed to the left upper limb also over the last six months. There was no history of sensory impairments during all these times. There was no history of trauma, neck pain, dysarthria, dysphagia, breathing difficulty, or bowel and bladder involvement. He did not have any previous comorbidities or neurological disorders. There was no history of any similar illness in his family. During this period, he had taken only vitamin supplements and no specific drug for the illness.

On examination, the upper limbs had spasticity in elbow and wrist flexors bilaterally, variable degrees of power deficits with more weakness of the first dorsal interosseous and wrist flexors and right deltoid with severe wasting of bilateral hand and forearm muscles, fasciculation of bilateral forearm and arm muscles along with exaggerated deep tendon reflexes [Table/Fig-1a,b].



[Table/Fig-1]: Wasting of thenar muscles: (a) and dorsal interossei; b) shown by blue arrow.

Lower limb examination revealed spasticity in the right hip and knee flexors, and exaggerated deep tendon reflexes bilaterally with fasciculation in bilateral thigh muscles without wasting and power deficits. Cranial nerves, sensory system, and cerebellar examinations were within normal limits.

Functional assessment revealed difficulty in holding small objects, writing and combing, and lifting weights more than 5 kg.

Laboratory tests, including electrolytes, blood glucose, cobalamin, kidney, liver, and thyroid functions, were within normal limits.

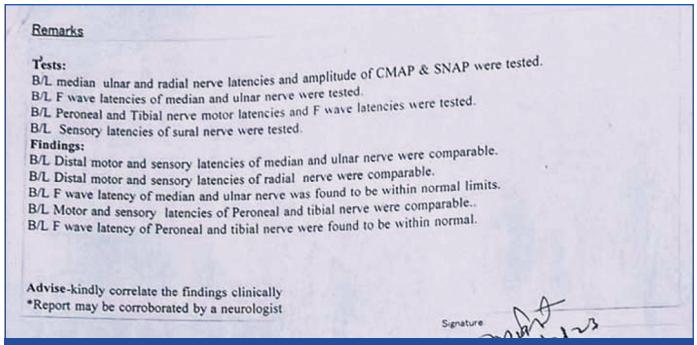
Electrophysiological evaluation was performed to assess the integrity of motor and sensory pathways.

Nerve Conduction Study (NCS) of the upper limbs, including the radial, ulnar, and median nerves, as well as the lower limb peroneal and tibial nerves, showed normal distal latencies, conduction velocities, and Compound Muscle Action Potential Amplitudes (CMAP). Sensory Nerve Action Potential (SNAP) was comparable, indicating preserved normal sensation.

In contrast, needle Electromyography (EMG) demonstrated widespread neurogenic changes. Multiple muscles from both upper and lower limbs and thoracic paravertebral muscles showed abnormal spontaneous activity in the form of fibrillation potentials, fasciculations, and positive sharp waves. On volitional activation, there was evidence of reduced recruitment of motor unit action potentials with an altered interference pattern, reflecting ongoing denervation and reinnervation [Table/Fig-2a,b].

A dynamic Magnetic Resonance Imaging (MRI) of the cervical spine was done, which was also found to be normal [Table/Fig-3].

Differential diagnosis of multifocal motor neuropathy, compressive myelopathy, Hirayama disease and JALS was considered. The possibility of multifocal motor neuropathy was excluded by the absence of conduction blocks in the NCS. Since the MRI had no features suggestive of compressive myelopathy or Hirayama



Remarks

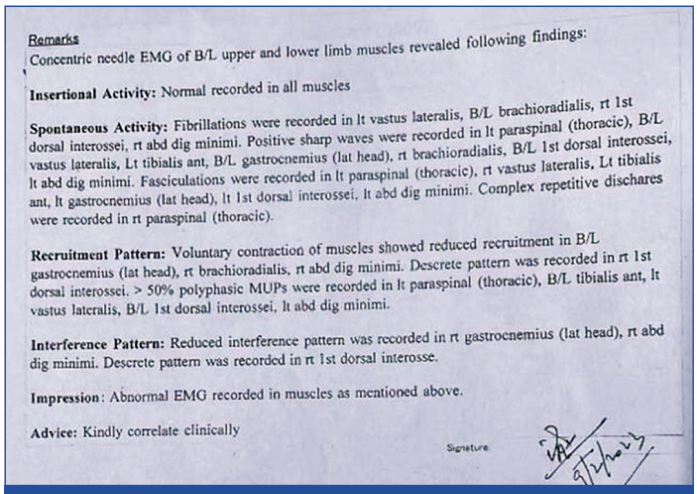
Tests:
B/L median ulnar and radial nerve latencies and amplitude of CMAP & SNAP were tested.
B/L F wave latencies of median and ulnar nerve were tested.
B/L Peroneal and Tibial nerve motor latencies and F wave latencies were tested.
B/L Sensory latencies of sural nerve were tested.

Findings:
B/L Distal motor and sensory latencies of median and ulnar nerve were comparable.
B/L Distal motor and sensory latencies of radial nerve were comparable.
B/L F wave latency of median and ulnar nerve was found to be within normal limits.
B/L Motor and sensory latencies of Peroneal and tibial nerve were comparable..
B/L F wave latency of Peroneal and tibial nerve were found to be within normal.

Advise-kindly correlate the findings clinically
*Report may be corroborated by a neurologist

Signature

[Table/Fig-2a]: Nerve conduction study showing motor and sensory conduction parameters of the upper limb (radial, ulnar, and median nerves) and lower limb (peroneal and tibial nerves). Findings were within normal limits.



Remarks

Concentric needle EMG of B/L upper and lower limb muscles revealed following findings:

Insertional Activity: Normal recorded in all muscles

Spontaneous Activity: Fibrillations were recorded in lt vastus lateralis, B/L brachioradialis, rt 1st dorsal interossei, rt abd dig minimi. Positive sharp waves were recorded in lt paraspinal (thoracic), B/L vastus lateralis, Lt tibialis ant, B/L gastrocnemius (lat head), rt brachioradialis, B/L 1st dorsal interossei, lt abd dig minimi. Fasciculations were recorded in lt paraspinal (thoracic), rt vastus lateralis, Lt tibialis ant, lt gastrocnemius (lat head), lt 1st dorsal interossei, lt abd dig minimi. Complex repetitive discharges were recorded in rt paraspinal (thoracic).

Recruitment Pattern: Voluntary contraction of muscles showed reduced recruitment in B/L gastrocnemius (lat head), rt brachioradialis, rt abd dig minimi. Descrete pattern was recorded in rt 1st dorsal interossei. > 50% polyphasic MUPs were recorded in lt paraspinal (thoracic), B/L tibialis ant, lt vastus lateralis, B/L 1st dorsal interossei, lt abd dig minimi.

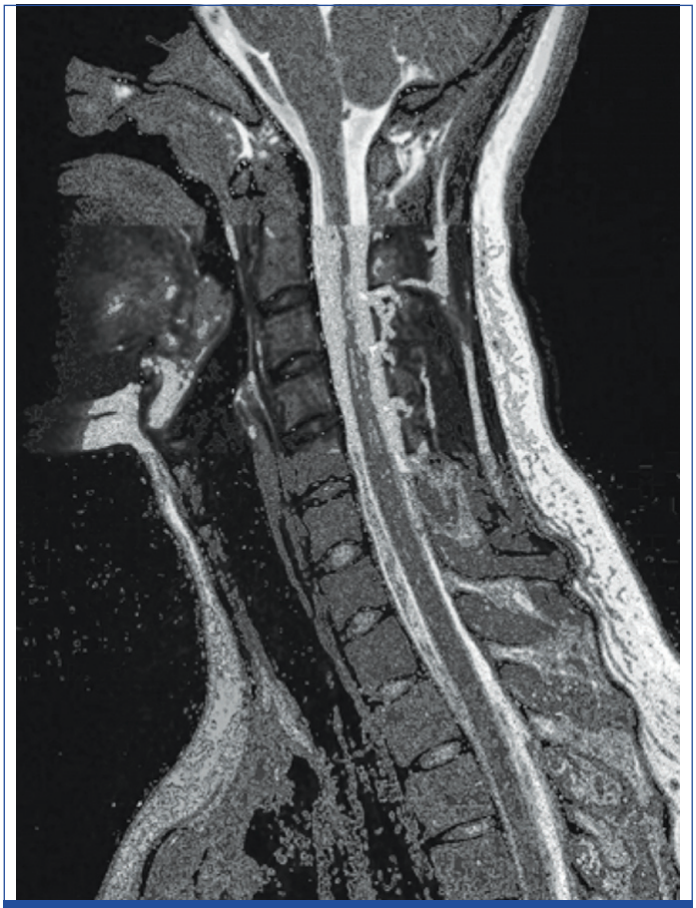
Interference Pattern: Reduced interference pattern was recorded in rt gastrocnemius (lat head), rt abd dig minimi. Descrete pattern was recorded in rt 1st dorsal interosse.

Impression: Abnormal EMG recorded in muscles as mentioned above.

Advice: Kindly correlate clinically

Signature

[Table/Fig-2b]: Needle Electromyography (EMG) of bilateral upper and lower limb muscles demonstrating abnormal spontaneous activity (fibrillations, fasciculations, and positive sharp waves) with reduced recruitment and interference patterns, consistent with neurogenic involvement.



[Table/Fig-3]: MRI of cervical spine.

disease, those diagnoses were excluded. Hence, the diagnosis of ALS was made as per El Escorial criteria [1] due to the presence of both Lower Motor Neuron (LMN) and Upper Motor Neuron (UMN) signs in clinical examination and EMG findings. And, as the age of the patient was less than 25 years, it was Juvenile ALS (JALS).

The patient was counselled regarding the poor prognosis and life-limiting nature of the illness and further progression of symptoms and plan of management. He was informed regarding the effects and cost of Riluzole and started on Riluzole 50 mg BD, which primarily acts by inhibiting the release of glutamate, and multivitamins. Non-pharmacological management included stretching and strengthening exercises, hand function improvement activities, and deep breathing exercises. A 10-15 repetitions of Isotonic strengthening exercises of bilateral upper and lower limbs along with core was advised for a duration of 45-60 minutes a day for 3-4 days a week.

Static and dynamic stretching exercises of spastic muscles with repetition of each stretch five times per session were advised for a total duration of 15-30 minutes a day for 2-3 days a week. Adaptive devices like the Universal cuff and built-up pen were given for Activities of Daily Living (ADL) improvement and the use of gloves and ice dunks for hands was suggested for sweating-associated concerns. Patient was reviewed after two months and was noted to have a reduction in spasticity and sweating along with improved activities of daily living.

DISCUSSION

ALS involves neurodegeneration of both upper and lower motor neurons and if it occurs before the age of 25, then it is called JALS.

The disease shows considerable variability in clinical presentation and survival, but the hallmark remains degeneration of upper and lower motor neurons [2]. In India, ALS prevalence is estimated at 3-5 per 100,000, with an annual incidence of 1.5-2.7 per 100,000 [3].

ALS was once thought to be solely a motor disease; however, it is now becoming more widely recognised that non-motor symptoms can also appear. The most widely recognised pathology is that glutamate excitotoxicity, oxidative stress, and eventually axonal damage result in a loss of control over the involuntary muscles [4].

JALS is a progressive neurodegenerative illness associated with specific gene mutations that impact motor neurons in the cerebral cortex, spinal cord, and brain stem. As of now, there are many known genetically defined types of JALS. ALS2 is an autosomal recessive form of ALS that develops slowly and in childhood. Bulbar or sensory abnormalities are absent in the autosomal dominant form of ALS4, which is characterised by pyramidal symptoms, slow progression, and severe muscle weakening. The hallmark of ALS5, a third variety that initially affects the hands and feet before spreading to the bulbar area, is lower motor neuron weakness [5].

Furthermore, Adult-Onset Amyotrophic Lateral Sclerosis (AO-ALS) and JALS are very different. First, the genetic contribution to JALS is greater than that of AO-ALS, with specific gene mutations accounting for approximately 40% of cases [6]. The genes most frequently associated with JALS are FUS, SETX, and ALS2, followed by SPG11, SOD1, SPTLC1, UBQNL2, and SIGMAR1. Second, the prognosis and disease course of JALS vary depending on the gene mutation and can be either very aggressive or more indolent. In contrast, most AO-ALS has an aggressive course with mortality within two to three years. Third, cases of JALS may manifest syndromically, impacting many areas of the central or peripheral nervous system, in addition to motor neuron degeneration [7].

Autonomic dysfunction in ALS starts with vagal disruption, followed by enhanced sympathetic activity, and eventually sympathetic denervation with vagal predominance. There is evidence for the subclinical involvement of both the sympathetic and parasympathetic nervous systems in ALS. However, clinically significant autonomic disturbances are infrequent and rarely noted in early ALS. In later stages, commonly reported ones are orthostatic hypotension or

postural dizziness. Our patient presented with initial symptoms of regional hyperhidrosis, which were followed by weakness, wasting, and spasticity of the same extremity, which later became generalised. In a research conducted by Beck M et al., on adult ALS patients, they found that individuals in the early phases of ALS exhibited palmar hyperhidrosis, but in later stages of the disease, they had hypohidrosis [8]. A case report by Chen X et al., described a young female patient with a five-month history of progressive limb weakness. Other than the classical motor features, she also showed palmar and plantar hyperhidrosis, which was atypical in the context of motor neuron disease. Neurological examination revealed evidence of both upper and lower motor neuron findings, consistent with motor neuron disorder findings. EMG study revealed widespread denervation, characteristic of ALS. An iodine-starch test and Sympathetic Skin Response (SSR) testing further supported autonomic involvement. Genetic testing with whole-exome sequencing was performed, which identified a heterozygous FUS P525L mutation in the case. Management was initiated with riluzole as a disease-modifying therapy. Supportive care included rehabilitation strategies to maintain mobility and independence, as well as topical treatment for hyperhidrosis to address the autonomic symptoms [9].

Hyperhidrosis, a condition that causes excessive sweating, is non-physiological and is also debilitating for patients. It is mediated by the sympathetic system of the body, which normally controls the homeostatic cooling mechanism. Primary idiopathic hyperhidrosis affecting palms, craniofacial areas, soles, and axillae occurs mainly during childhood and could be influenced by thermal, vasodilatory, and emotional stimuli [10]. Secondary hyperhidrosis is due to various systemic causes, major pathologies being endocrine, neuroendocrine, neurological, or malignancies.

In search of the pathophysiology behind this, Chida K et al., found an enhanced sympathetic function and reduced parasympathetic function in the early stages of ALS [11], while Shindo K et al., observed an elevated firing rate in sympathetic nerve activity among mildly impaired ALS patients in comparison to other neuromuscular disorders [12]. Whereas, in more advanced stages, a diminished sweat rate indicates a continuous decline of the sudomotor system due to the degeneration of the intermediolateral nucleus, leading to central sympathetic failure, alongside the degeneration of peripheral sympathetic nerves. Furthermore, the deterioration of postganglionic parasympathetic fibers may result in the atrophy of sweat glands, all leading to hypohidrosis.

CONCLUSION(S)

This case throws light on the concept of ALS as a multisystem disease: in such a case, hyperhidrosis may represent a pre-motor manifestation of ALS and not an occasional finding. So, it is important to consider the possibility of motor neuron disease in young individuals with progressive unilateral neurological deficits and also in those presenting with autonomic dysfunctions.

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