INJ
МІЖНАРОДНИЙ НЕВРОЛОГІЧНИЙ ЖУРНАЛ
INTERNATIONAL NEUROLOGICAL JOURNAL

ПРАКТИКУЮЧОМУ НЕВРОЛОГУ
TO PRACTICING NEUROLOGIST

UDC 616.74-005.1-092.9:575.22-056.7 DOI: https://doi.org/10.22141/2224-0713.21.1.2025.1152

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Adult-onset spinal muscular atrophy in a patient with *SOD1* mutation: case report

For citation: International Neurological Journal (Ukraine).2024;21(1):64-68. doi: 10.22141/2224-0713.21.1.2025.1152

Abstract. *Amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA) are distinct motor neuron disorders with overlapping molecular mechanisms. ALS involves progressive upper and lower motor neuron degeneration, while SMA primarily affects lower motor neurons. Mutations in SOD1 (superoxide dismutase 1), a well-established cause of familial ALS, have been identified in patients with atypical motor neuron disease phenotypes, suggestive of their broader role in motor neuron dysfunction. A 28-year-old male presented with progressive distal muscle weakness, atrophy, and a steppage gait, without upper motor neuron involvement. Electromyography confirmed chronic motor neuron dysfunction, raising suspicion of SMA. Genetic testing excluded SMN1 deletions but identified a pathogenic SOD1 mutation. Despite this, slow disease progression and phenotype were more consistent with adult-onset SMA type IV than ALS. This case highlights the diagnostic challenges posed by overlapping features of ALS and SMA. The findings emphasize the need for further research into the clinical features associated with SOD1 mutations and their potential contributions to SMA-like presentations, refining our understanding of motor neuron disorders.*
Keywords: *motor neuron disease; amyotrophic lateral sclerosis; spinal muscular atrophy; SOD1*

Introduction

Amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA) are distinct motor neuron disorders with overlapping clinical features. Both involve motor neuron dysfunction and loss, leading to progressive muscle weakness and atrophy [1]. ALS, or Lou Gehrig's disease, is a neurodegenerative disorder affecting upper and lower motor neurons, causing progressive weakness and reduced survival [2]. While most ALS cases are sporadic, 5–10 % are familial, with approximately 20 % of these linked to *SOD1* (superoxide dismutase 1) mutations [2]. In contrast, SMA is caused by mutations in the *SMN1* (survival motor neuron 1) gene on chromosome 5q13, leading to insufficient SMN protein, which is critical for motor neuron function. The severity of SMA is determined by the copy number of *SMN2*, a paralog of *SMN1* that partially compensates for its loss by producing small amounts of functional SMN protein. A higher number of *SMN2* copies is linked to milder disease phenotypes, with SMA classified into types I–IV based on the age of onset and clinical progression [3].

Though primarily linked to familial ALS, *SOD1* mutations have also been investigated for their potential influence on molecular pathways shared with other motor neuron disorders. Experimental studies suggest that *SOD1* mutations, a cause of familial ALS, may impact SMA-related pathways. ALS mouse models show that mutant *SOD1* disrupts SMN protein function, while restoring SMN levels mitigates motor neuron loss and delays symptoms, highlighting potential mechanistic overlap [4]. These findings suggest that mutations in *SOD1* may influence motor neuron dysfunction beyond classical ALS phenotypes.

Here, we present the case of a patient with adult-onset SMA type IV harbouring a rare *SOD1* mutation (c.260A>G). While this mutation is predominantly linked to ALS, the patient's clinical presentation defined by slow progression and a lack of upper motor neuron signs is more well-aligned with the characteristic features of SMA.

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Case description

The patient, a 28-year-old male, first presented with distal lower limb weakness in 2019 at the age of 23, initially characterized by difficulties standing on his toes. Over the next three years, the weakness gradually progressed, spreading to the proximal lower limbs and leading to challenges with climbing stairs and rising from a squat. Muscle atrophy extended to the calves, feet, thighs, shoulders, and small muscles of the hands, resulting in difficulties with fine motor tasks. These symptoms were accompanied by intermittent cramps, fasciculations, and gait disturbances. In 2022, a neurological assessment was performed as the symptoms persisted. Electromyography (EMG) revealed chronic motor neuron damage in the anterior horns of the spinal cord, and serum creatine kinase levels were elevated at 1168 U/L (normal range: 39–308 U/L), suggesting neuromuscular involvement. However, no further diagnostic tests were performed at that time, and the patient's condition continued to evolve.

By May 2024, the patient presented with worsening weakness in both hands, impaired gait, and pronounced muscle atrophy, which eventually led to further evaluation at Kyiv City Clinical Hospital No. 11. Neurological examination revealed moderate tetraparesis, more prominent in the lower extremities, accompanied by hypotrophy in the hands and calves. Reflexes were diminished in both upper and lower limbs, and fasciculations were noted in the back and proximal limb muscles. The patient exhibited a steppage gait. Repeat EMG confirmed chronic motor neuron damage at cervical, thoracic, and lumbar levels, raising suspicion of SMA. Magnetic resonance imaging revealed degenerative changes but no structural lesions to account for the motor neuron pathology. Serum creatine kinase levels were further elevated at 1350.6 U/L. Based on these findings, a provisional diagnosis of SMA type IV was made, with genetic testing for *SMN1* and *SMN2* deletions recommended, alongside repeat EMG and ongoing neurological follow-up.

In October 2024, genetic testing at the OHMADYT Centre for Orphan Diseases identified a heterozygous pathogenic variant in the *SOD1* gene: c.260A>G (p.Asn87Ser). This mutation has been observed in both autosomal recessive juvenile-onset ALS and autosomal dominant ALS [5–7]. However, the clinical presentation was inconsistent with ALS, prompting the need for further assessments. Genetic analysis of *SMN1* and *SMN2* revealed no deletions, complicating confirmation of SMA but not entirely excluding it, as point mutations and rare variants were not assessed. Additionally, Kennedy's di-

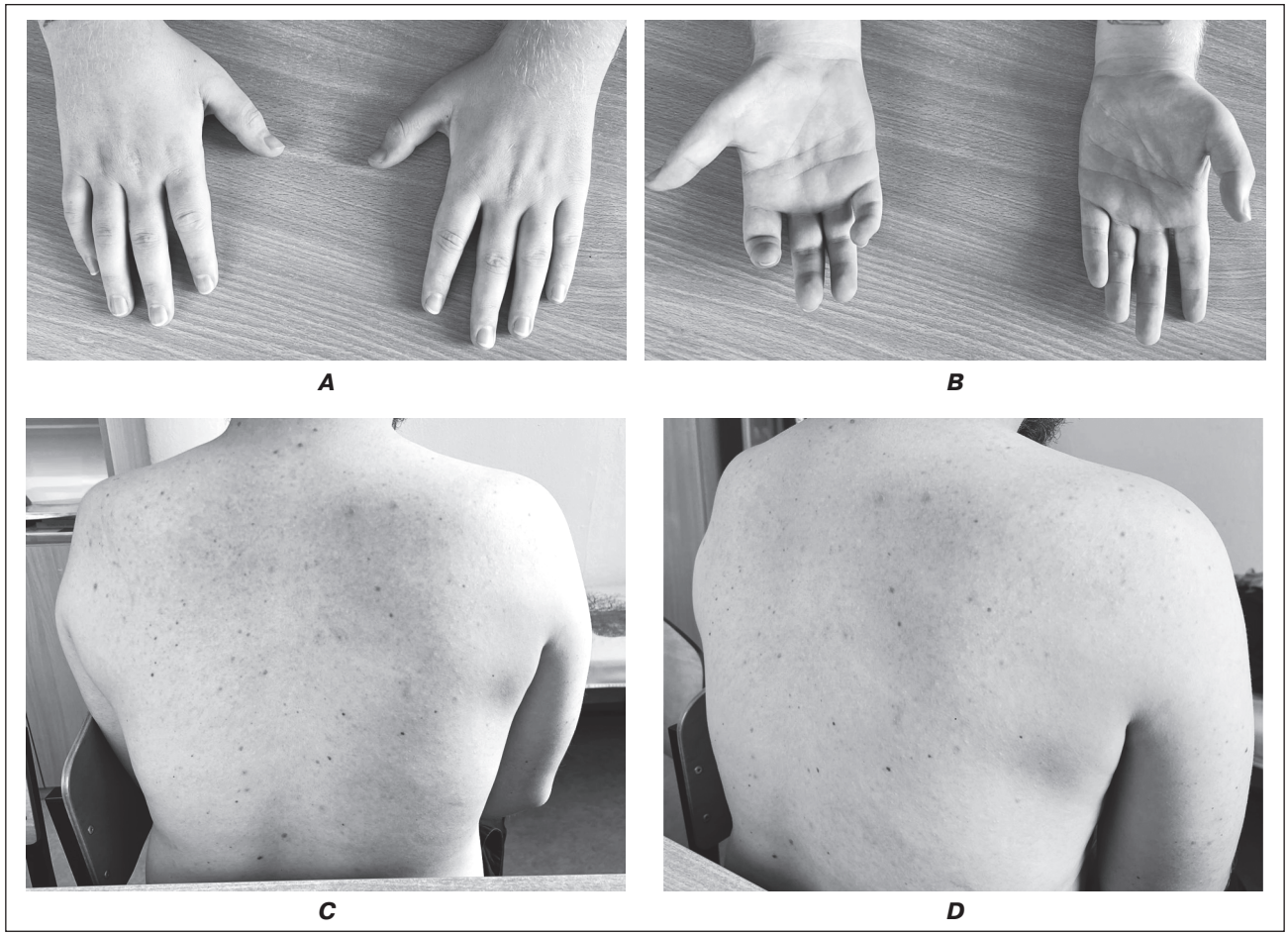

Figure 1. Clinical features. Muscle atrophy observed in the dorsal and palmar aspects of the hand (A, B), shoulder and back muscles (C, D)

sease was excluded through genetic testing, which confirmed the absence of CAG repeat expansions in the AR (androgen receptor) gene.

In November 2024, the patient was referred to the Neurology Department of the Bogomolets National Medical University for additional clinical evaluation due to the complexity of the case. Examination revealed a steppage gait and the use of a "ladder" technique to rise from a sitting position, often suggestive of myopathic or motor neuron disorders. Muscle strength evaluated on the Medical Research Council scale showed scores of 3.5 in the hands, 2.5 in the shoulders, 2 in the feet, and 4 in the calves and thighs. Fasciculations were noted in the proximal upper limb muscles, reflexes were diminished across all limbs, muscle tone was normal with no evidence of spasticity, and sensory function was preserved. Differential diagnoses included polyneuropathy, ALS, and myopathy. Polyneuropathy was excluded due to preserved sensory function, ALS was ruled out based on the absence of upper motor neuron signs such as spasticity and hyperreflexia, and myopathy was excluded due to the neurogenic pattern observed in EMG findings. Despite the absence of *SMN1* deletions, the patient's pattern of progressive weakness, slow clinical course, and lack of upper motor neuron signs aligned more closely with adult-onset SMA type IV, leading to a clinical diagnosis of SMA type IV.

Discussion

This case highlights the challenges of diagnosing motor neuron disorders with atypical clinical and genetic findings. The initial clinical presentation and EMG findings suggested SMA type IV, but the absence of deletions in *SMN1* and the discovery of a heterozygous pathogenic *SOD1* mutation, typically associated with ALS, introduced significant diagnostic uncertainty. These complexities reflect the need to explore the limitations of current diagnostic methods and the potential overlap between SMA- and ALS-associated mechanisms, as discussed in the following sections.

Although no deletions in *SMN1* exons 7 and 8 were identified via MLPA analysis, it is important to note the limitations of this method. While MLPA reliably identifies deletions responsible for approximately 96.4 % of 5q SMA cases, it cannot detect the remaining 3.6 % of cases involving subtle mutations such as a point mutation on one chromosome combined with a deletion or gene conversion on the other [3]. Additionally, the absence of SMN protein measurement in this patient leaves the possibility of functional SMN deficiency unresolved, highlighting the challenge of definitively excluding *SMN1*-related SMA in atypical presentations.

Most SMA cases are linked to *SMN1* mutations, but a smaller subset, classified as non-5q SMA, accounts for approximately 5 % of cases. These disorders, involving other genes implicated in motor neuron dysfunction, are unrelated to *SMN1* mutations but share overlapping features with both 5q SMA and ALS, further complicating diagnosis. For instance, Finkel type SMA (linked to *VAPB*) and Jokela type SMA (associated with *CHCHD10*) exhibit progressive proximal muscle weakness, resembling SMA type IV [8]. However, genetic testing in our patient did not reveal mutations in any known non-5q SMA-related genes, underscoring the diagnostic ambiguity and the evolving understanding of non-5q SMA etiology. Kennedy's disease, or spinal and bulbar muscular atrophy, was also excluded through genetic testing that revealed no expansions in the AR gene. While Kennedy's disease shares features such as pure lower motor neuron symptoms and proximal weakness, its hallmark systemic manifestations, including endocrinopathies, were absent in this patient [8].

The identification of a *SOD1* mutation introduces another layer of complexity, raising questions about its potential role in SMA-like presentations. Experimental studies have shown that mutant *SOD1* disrupts SMN protein function in ALS mouse models, and restoring SMN levels mitigated motor neuron loss and delayed symptom onset [4]. Additionally, co-transfection studies in NSC34 cells revealed that SMN protects against cell death induced by mutant *SOD1* under oxidative stress, potentially through its chaperone activity, which prevents protein aggregation [9]. Mutations in SMN or its suppression by shRNA significantly reduced this protective effect, emphasizing the interplay between SMN and SOD1 in motor neuron survival [9]. Furthermore, reduced SMN levels have been observed in the spinal cord of ALS patients and SOD1(G93A) mouse models, where overexpression of SMN improved locomotor function and rescued motor neurons, though survival benefits were limited by SMN mislocalisation caused by mutant *SOD1* [10]. Similarly, clinical data indicate that lower SMN protein levels, influenced by *SMN1* and *SMN2* copy numbers, increase ALS susceptibility and worsen disease progression [11]. These insights suggest a functional overlap between *SOD1* and SMA-associated pathways, expanding our understanding of motor neuron dysfunction beyond classical ALS.

Interestingly, in cases with SMA-like symptoms but no *SMN1* mutations, a subset of patients was found to carry mutations in ALS-associated genes, including *SOD1* and *FUS*, implying that these mutations may contribute to SMA-like syndromes [12]. Supporting this, a case report described a 63-year-old female with a novel *SOD1* mutation (c.358G>C, p.V120L) who was clinically diagnosed with SMA. Her presentation of symmetrical distal weakness, steppage gait, and absence of upper motor neuron signs resembled SMA rather than classical ALS, with slow disease progression aligning her phenotype with SMA type IV [13]. Electromyographic findings confirmed a chronic neurogenic process without evidence of primary myopathy, mirroring features observed in our patient. Both cases exhibited slow disease progression and lacked hallmark ALS signs, challenging traditional genotype-phenotype correlations for *SOD1* mutations [13].

The *SOD1* c.260A>G mutation identified in our patient has also been previously reported in ALS cases from Iranian, Pakistani, and Japanese families, demonstrating notable clinical variability. Age of onset in these cases ranged from 13 to 52 years, with survival times spanning weeks to

over a decade. For example, in the Iranian case, symptoms began at age 34 with lower extremity weakness, while survival outcomes varied widely even within the same genetic background [5–7]. In contrast, our patient, who carries the same *SOD1* mutation, exhibited a distinctly SMA-like phenotype characterized by slow progression, selective distal atrophy, and the absence of upper motor neuron signs. This divergence highlights the potential for certain *SOD1* mutations to manifest along a spectrum of motor neuron disorders, expanding the phenotypic variability associated with SOD1.

These findings collectively highlight the intricate relationships between genotype and phenotype in *SOD1* mutations. They emphasize the need for further research into the potential overlap between SMA and ALS mechanisms and the broader genetic and environmental factors shaping motor neuron disorder presentations.

Conclusions

This case highlights diagnostic challenges of motor neuron disorders due to the phenotypic overlap. While the absence of *SMN1* deletions, the slow progression of symptoms, and the presence of a *SOD1* mutation collectively suggest that this patient's phenotype aligns more closely with SMA type IV, the exact contribution of the *SOD1* mutation remains unclear. Further research is essential to elucidate the role of *SOD1* mutations in SMA-like presentations and their interplay with SMN pathways. A better understanding of these shared molecular mechanisms could refine diagnostic criteria and open new avenues for targeted therapies in atypical motor neuron disorders.

Consent. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available upon request.

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Received 01.11.2024
Revised 14.12.2024
Accepted 12.01.2025

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Conflicts of interests. Authors declare the absence of any conflicts of interests and own financial interest that might be construed to influence the results or interpretation of the manuscript.

Information about funding. No funding. The work was performed in accordance with the scientific research work of the Neurology Department of the Bogomolets National Medical University.

Authors' contribution. M. Mykhailova (first author) — manuscript writing, data analysis; M. Prokopiv (senior author) — supervision, clinical management of the patient, diagnosis, study concept, manuscript finalization; T. Illyash — clinical diagnosis, patient observation, data collection, manuscript finalization.

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Спінальна м'язова атрофія з початком у дорослому віці в пацієнта з мутацією *SOD1*: клінічний випадок

Резюме. Бічний аміотрофічний склероз (БАС) та спінальна м'язова атрофія (СМА) є одними з найпоширеніших генетично обумовлених захворювань, які характеризуються ураженням мотонейронів. Для БАС типовим є прогресуюче ураження як верхніх, так і нижніх мотонейронів, тоді як СМА переважно вражає нижні мотонейрони. Однак іноді генетичні мутації, зокрема у гені *SOD1*, що зазвичай пов'язані з БАС, можуть викликати атипові прояви, ускладнюючи диференціальну діагностику. У цьому клінічному випадку 28-річний пацієнт звернувся зі скаргами на прогресуючу дистальну м'язову слабкість, атрофію та степажну ходу, без ознак ураження верхніх мотонейронів. Електроміографія підтвердила хронічну дисфункцію нижніх мотонейронів, що викликало підозру на СМА. Генетичне тестування не виявило делецій у гені *SMN1*, проте було ідентифіковано патогенну мутацію в гені *SOD1*. Однак клінічний перебіг захворювання, а саме повільне прогресування симптомів та відсутність ураження верхніх мотонейронів, був більш характерний для СМА IV типу з початком у дорослому віці, а не БАС. Цей випадок демонструє складність діагностики уражень мотонейронів при атипових клінічних і генетичних ознаках. Таким чином, підкреслюється необхідність глибокого генетичного аналізу й мультидисциплінарного підходу для точного встановлення діагнозу та кращого розуміння ролі мутацій *SOD1* у формуванні фенотипів, схожих на СМА.

Ключові слова: хвороба мотонейронів; бічний аміотрофічний склероз; спінальна м'язова атрофія; *SOD1*