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Amyotrophic lateral sclerosis associated with Sjögren's syndrome: a case report

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Abstract

Background Motor neuron disease (MND) is a chronic and progressive neurodegenerative disorder with an unknown cause. The development of amyotrophic lateral sclerosis (ALS) is believed to be linked to an immune response. Monocytes/macrophages and T cells are key players in the disease's advancement. Monitoring levels of cytokines in the blood can help forecast patient outcomes, while immunotherapy shows promise in alleviating symptoms for certain individuals.

Case presentation A 56-year-old male patient was admitted to the hospital due to progressive limb weakness persisting for eight months. The neurological examination revealed impairments in both upper and lower motor neurons, as well as sensory anomalies, without corresponding signs. Electrophysiological examination results indicated extensive neuronal damage and multiple peripheral nerve impairments, thereby the diagnosis was ALS. One month ago, the patient began experiencing symptoms of dry mouth and a bitter taste. Following tests for rheumatic immune-related antibodies and a lip gland biopsy, a diagnosis of Sjögren's syndrome (SS) was proposed. Despite treatment with medications such as hormones (methylprednisolone), immunosuppressants (hydroxychloroquine sulfate), and riluzole, the symptoms did not significantly improve, but also did not worsen.

Conclusion It is recommended to include screening for SS in the standard assessment of ALS. Furthermore, research should focus on understanding the immune mechanisms involved in ALS, providing new insights for the diagnosis and treatment of ALS in conjunction with SS.

Keywords Motor neuron disease, Amyotrophic lateral sclerosis, Sjögren's syndrome, Immunity, Nerve damage

Background

Amyotrophic lateral sclerosis (ALS) is the most common form of motor neuron disease (MND), a rare neurodegenerative disorder that progresses slowly. The global incidence is around 1.59 per 100,000 individuals annually [1], with a standardized annual incidence rate in China of 1.62 per 100,000 people [2]. ALS is characterized by the selective death of motor neurons in the brain and spinal cord, leading to progressive weakening and wasting of muscles throughout the body. Unfortunately, most patients die from respiratory failure within 2–4 years of symptom onset [3]. With the global population aging, it is projected that by 2040, approximately 380,000 individuals worldwide will have ALS [3]. At present, pharmaceutical treatments for ALS are limited in their ability to halt or reverse the disease progression [3]. A recent report by Grand View Research reveals that global spending on ALS treatment reached approximately $540 million in 2018. Projections suggest this figure will increase to $890 million by 2026, with a compound annual growth

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rate of 5.8% from 2019 to 2026. ALS, like other neurodegenerative disorders, is influenced by a combination of age-related issues, environmental factors, and genetic components. Currently, advancements in high-throughput sequencing technologies have identified over 60 genes linked to the development of ALS [4]. However, ongoing research continues to explore additional genetic factors. Furthermore, studies have shown that various molecular pathways play a significant role in the onset of ALS, including oxidative stress, excitotoxicity, neuroinflammation, glial dysfunction, mitochondrial dysfunction, compromised DNA damage and repair, dysregulated RNA metabolism, impaired protein homeostasis, and axonal damage, among others [5]. The exact cause and disease mechanism of ALS are still unknown. Currently, there are no definitive laboratory or imaging tests that can provide a clear diagnosis. Diagnosis primarily depends on the patient's medical history, clinical symptoms, and electrophysiological changes [1]. The limited treatment options for ALS can be likened to a death sentence for patients. Recent research has indicated that ALS often coexists with impairments in cognitive function, sensation, and the autonomic nervous system. Additionally, there are reports suggesting that ALS is frequently associated with other disorders such as Parkinson's disease, frontotemporal dementia, cervical spondylotic myelopathy, rheumatic immune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, and biliary cirrhosis), retinopathy, sleep disorders, and other conditions [6, 7]. Sjögren's syndrome (SS) is a chronic autoimmune disorder that primarily affects exocrine glands, leading to symptoms such as dry mouth and dry eyes due to dysfunction of salivary and lacrimal glands. Additionally, there is a potential for multi-organ involvement beyond these primary symptoms. Studies have shown that neurological impairment symptoms can be observed in a significant percentage of SS patients, ranging from 8.5 to 70% [8]. In a study by Delalande et al. involving 82 SS patients with neurological impairments, it was found that 47% of these patients had exhibited neurological manifestations six years prior to experiencing dry symptoms [9]. Among these, peripheral neuropathy is the most common neurological complication of Sjögren's syndrome (SS), primarily affecting sensory nerves. While central nervous system involvement is not as common (2–25%), it can manifest as focal cerebrospinal lesions (such as cerebral hemorrhage, aphasia, dysarthria, epileptic seizures, migraine, movement disorders, and syndromes related to cerebellar involvement). These lesions may be multifocal (mostly demyelinating lesions) or diffuse (resulting in cognitive dysfunction, dementia, mental abnormalities, and aseptic meningitis). The main clinical symptoms of ALS in combination with SS include weakness, muscle atrophy, and muscle twitching, typically observed in the hands and feet. Electrophysiological tests reveal abnormal motor nerve conduction and signs of acute denervation. The clinical presentation of motor neuron disease (MND) associated with SS resembles that of lower motor neuron disease, with upper motor neuron involvement being very rare. We recently admitted a patient with a dual diagnosis of ALS and SS, a condition that has been rarely reported in the medical literature. Through a literature review, we are analyzing and summarizing the clinical characteristics of this patient.

Case presentation

The 56-year-old male patient was admitted to the hospital on March 18, 2022, due to a history of left lower limb weakness for 8 months, left upper limb weakness for 3 months, and right lower limb weakness for 2 months. The initial symptoms of left lower limb weakness, characterized by dragging during walking and hip pain without numbness, prompted a visit to another hospital where he was diagnosed with 'left femoral bone hyperplasia.' Although treatment relieved the hip pain, the weakness in the left lower limb persisted. Subsequently, he experienced dizziness symptoms six months ago, described as a heavy head and mental fog, leading to a diagnosis of 'cerebral infarction' at another hospital. Despite some improvement in dizziness following treatment, the left lower limb weakness persisted. Three months ago, he developed left upper limb weakness, affecting his ability to hold objects steadily. Two months ago, the weakness in the left limb worsened and was accompanied by right lower limb weakness, necessitating the use of a crutch. Alongside these motor symptoms, he reported numbness and burning sensations in both feet, as well as sleep disturbances characterized by difficulty falling asleep, frequent awakenings, and vivid dreams. One month ago, he began experiencing dry and bitter mouth, with reduced thirst for water. Past medical history revealed no significant abnormalities. The patient has a personal history of smoking for over 40 years, consuming 20 cigarettes per day, and occasional drinking. There is no reported similar medical history among family members. Upon physical examination of the internal medicine system, dry tongue texture and flake-like shedding of teeth were noted, with no other obvious abnormalities. Neurological examination showed trans-threshold gait, significant muscle atrophy in the thenar and interosseous muscles of the left hand, and a positive left hand paper-holding test indicating weakened muscle strength in the ulnar 3 fingers. Measurements of lower leg circumference showed 10 cm for the left leg and 11 cm for the right leg (10 cm above the medial malleolus). As per the Medical Research Council (MRC) classification standard, the muscle strength in the proximal part of the left upper limb was graded at 4/5, while the distal part was graded at 3/5. The

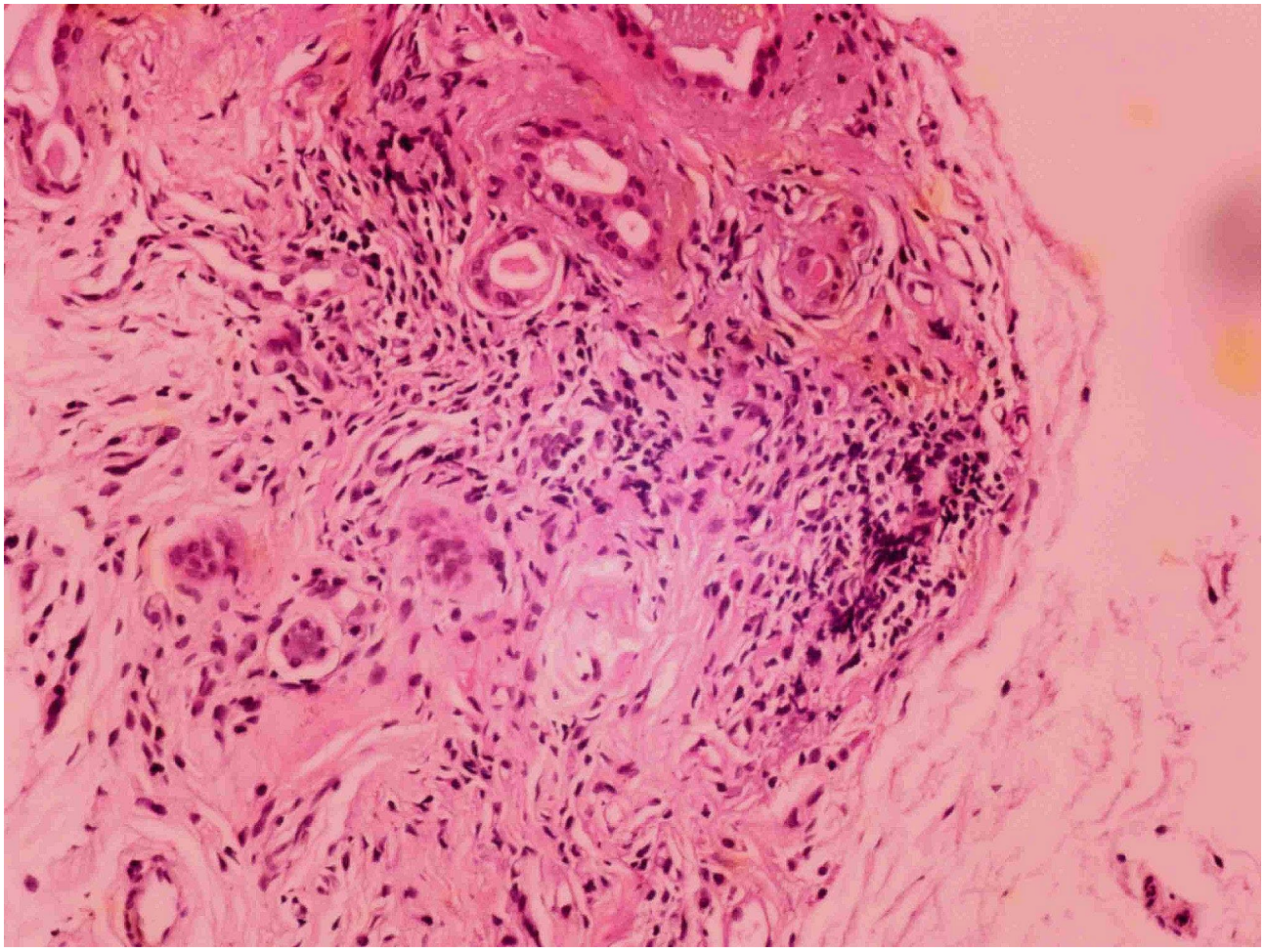

Fig. 1 (Labial glands) showed chronic inflammatory changes (Chisholm grade 3: lymphocyte infiltration in one focus, lobular structure of salivary glands was basically normal, and isolated acinar atrophy)

muscle strength in the lower limbs was graded at 4/5. A slight decrease in muscle tone was noted in the left limb. Active reflexes were observed in the biceps brachii, triceps brachii, and radial periosteum. The Hoffmann sign in the left upper limb was positive, with hyperactive knee reflexes and Achilles tendon reflexes. Fasciculation phenomena were present in the left upper limb and both lower limbs. Positive findings included patellar clonus, ankle clonus, and bilateral Babinski sign. Laboratory test results are detailed as follows: In the blood routine, the monocytes absolute value is 0.68×10^9/L (reference range: $0.1–0.6\times10^9$/L), and the total platelet count is 374×10^9/L (reference range: $100–300\times10^9$/L); for electrolytes, the potassium content is 3.4 mmol/L (reference range: 3.5–5.3 mmol/L), and the calcium level is 2.13 mmol/L (reference range: 2.2–2.7 mmol/L); in terms of liver function indicators, the total bile acid is 10.74 μmol/L (reference range: 0.14–9.66 μmol/L), total protein is 55.2 g/L (reference range: 56–85 g/L), and albumin is 35.1 g/L (reference range: 40–55 g/L); regarding kinase-related aspects, creatine kinase is 276 U/L (reference range: 38–174 U/L); additionally, 25-hydroxyvitamin D is 17.3 ng/ml (reference range: 30 ng/ml); anti-nuclear antibodies and anti-nuclear antibody spectra show: Anti-SSA antibody +++, Anti-RO-52 antibody +++, Anti-nuclear antibody (ANA) 1:100 is positive, ANA 1:320 is positive, and ANA 1:1000 is weakly positive; Lumbar puncture results showed colorless and transparent cerebrospinal fluid with a cerebral pressure of 160mmH2O, cerebrospinal fluid biochemistry revealed a quantitative protein level of 676 mg/L (reference range: 200–400 mg/L); Serum and cerebrospinal fluid paraneoplastic 14 items examination (anti-Titin antibody, anti-Recoverin antibody, anti-PKCγ antibody, anti-GAD65 antibody, anti-Zic4 antibody, anti-Tr(DNER) antibody, anti-SOX1 antibody, anti-Ma2 antibody, anti-Ma1 antibody, anti-Amphiphysin antibody, anti-CV2 antibody, anti-Ri antibody, anti-Yo antibody, anti-Hu antibody) were all negative; Erythrocyte sedimentation rate, anemia trio (ferritin, vitamin B12, folic acid), immunoglobulin (immunoglobulin A, G, M, E, complement

C3, C4), rheumatoid factor, and anti-neutrophil cytoplasmic antibodies (c-ANCA, p-ANCA, anti-GBM antibody, anti-PR3 antibody, anti-MPO antibody) exhibited no abnormalities. Chest CT reveals the presence of double lung emphysema with multiple bullae in the subpleural area, along with a calcification shadow in the anterior segment of the right upper lung and a small amount of fibrosis in the right lower lung. Cervical MRI arteriovenous angiography (MRA) shows a predominant right vertebral artery, while the cervical MRI plain scan indicates cervical degenerative changes. Thoracic MRI displays thoracic degenerative changes, and lumbar MRI notes degenerative alterations in the lumbar spine with spinal canal stenosis. Cranial MRI plain scan, cranial MRA, DWI, and PWI do not detect any abnormalities in the brain, with no abnormal signal in the cranial DWI and no abnormalities in the intracranial arteries according to MRA. PWI reveals a slight decrease in regional cerebral blood flow in the left cerebellum. Limb nerve conduction function examination suggests extensive neurogenic damage, possibly originating from the anterior horn of the spinal cord, along with multiple peripheral nerve damages affecting both sensory and motor fibers (see Tables 1, 2, 3). Biopsy pathology of the lip gland shows chronic inflammatory changes (Chisholm grade 3) characterized by lymphocyte infiltration, essentially normal salivary gland lobule structure, and isolated acinar atrophy (Fig. 1). The patient declined to further undertake the genetic test for MND on account of economic factors. The patient was diagnosed with MND, specifically ALS, and SS. Treatment included intravenous administration of methylprednisolone 40 mg daily for anti-inflammatory purposes, along with measures to enhance microcirculation, nourish nerves, improve sleep, acupuncture, and physical therapy. Upon discharge, the patient continued with oral prednisone 40 mg daily for anti-inflammatory effects, hydroxychloroquine sulfate 200 mg twice daily to suppress immunity, and oral riluzole 50 mg twice daily. One month post-discharge follow-up showed no significant change in limb weakness symptoms, with the patient still experiencing sleep disturbances, numbness, and a burning sensation in both feet.

Discussion

Alongside the continuous intensification of the aging population process, the incidence of ALS is progressively escalating. Given the substantial population base of our country, the prevalence of ALS is rather high, and this disease generates significant troubles for patients, families, and society. Since the underlying pathophysiological mechanism of ALS remains indistinct, the clinical manifestations exhibit heterogeneity and there is a dearth of effective treatment modalities, this constitutes a pain point in the clinical diagnosis and treatment of

Table 1 Sensory nerve conduction studies

Nerve	Latency (ms)	Amplitude (μV)	Distance (mm)	Conduction velocity (m/s)
Median nerve (L) Digit II–wrist	3.8 (reference range: <3.5)	1.9 (reference range: >3.0)	176 (reference range: 7 cm)	46 (reference range: >45)
Ulnar nerve (L) Digit V–wrist	3.49 (reference range: <3.1)	0.87 (reference range: >3.0)	162 (reference range: 14 cm)	46 (reference range: >44)
Superficial peroneal nerve (R) Digit I–ankle	4.01 (reference range: 3.4 ± 0.4)	1.0 (reference range: >1.0)	151 (reference range: 14 cm)	38 (reference range: >40)
Sural nerve (R) Calf–fibular head	4.17 (reference range: <3.8)	3.5 (reference range: >3.0)	145 (reference range: 14 cm)	35 (reference range: >40)
Superficial peroneal nerve (L) Digit I–ankle	4.27	0.32	145	34
Sural nerve (L) Calf–fibular head	3.75	3.9	140	37

Table 2 Needle Pole electromyography

Muscle	Spontaneous		Motor unit potential	
	Positive shape wave	Fibrillation potential	Duration (ms)	Amplitude (μV)
Extensor digitorum brevis muscle (R)		++	19.4 (reference range: 9.3–12.9)	292 (reference range: 391–661)
Abductor hallux abductor muscle (R)	++	+	13.8 (reference range: 9.4–13.4)	155 (reference range: 387–656)
Tibialis anterior muscle (R)	++		27.7 (reference range: 9.7–13.9)	317 (reference range: 407–684)
Gastrocnemius muscle (medial head) (R)	++		35.8 (reference range: 8.6–13.2)	258 (reference range: 396–675)
Intramedullary thigh muscle (R)	++	+	30.7 (reference range: 9.8–13.8)	341 (reference range: 382–645)
Extensor digitorum brevis muscle (L)	++	+	27.2	468
Abductor hallux abductor muscle (L)	++	+	19.0	553
Tibialis anterior muscle (L)	+++		33.8	232
Gastrocnemius muscle (medial head) (L)	++		49.3	355
Intramedullary thigh muscle (L)	+			
Abductor pollicis brevis muscle (L)		++	35.4 (reference range: 8.9–13.0)	554 (reference range: 381–651)
Abductor digiti minora muscle (L)	++	++	24.7 (reference range: 8.4–12.0)	145 (reference range: 369–632)
Biceps brachii muscle (L)	++	+	18.9 (reference range: 9.2–13.2)	300 (reference range:322–557)
Deltoid muscle (middle) (L)	+			
L4 paraspinal muscle (R)	++			
L4 paraspinal muscle (L)	+	+		
S1 paraspinal muscle (L)	+			
T3 paraspinal muscle (R)				
T5 paraspinal muscle (L)		++		

ALS. Investigating the pathogenesis of ALS can support the development of treatment methods, slow disease progression, and improve patient quality of life. Additionally, enhancing clinical management of ALS patients is crucial. Analyzing clinical data and summarizing disease characteristics provide a basis for standardized diagnosis and treatment. Epidemiological studies have shown that 11.7% of MND patients can identify clear causes during follow-up and are eventually diagnosed with MND syndrome [10].

In the realm of basic research on ALS, apart from genomics and genetics, abnormal protein metabolism, cellular and synaptic pathological alterations. Neuroimmune and inflammation are also among the pathogenic mechanisms of ALS and, simultaneously, an important therapeutic target [11]. A study by Japanese scholars Yamanaka et al. revealed a negative correlation between the presence of abnormally activated astrocytes and the survival time of ALS model mice. Furthermore, they found that the beta-interferon TIR domain-containing adaptor protein, which is associated with innate immunity, has the ability to eliminate abnormal glial cells, thereby offering brain protection [12]. American scholars Zhao et al. disclosed that M2 macrophages differentiated from monocytes originated from ALS-induced pluripotent stem cells can restrain the release of pro-inflammatory cytokines mediated by M1 macrophages, inhibit the proliferation of cytotoxic T cells, and induce their transformation into regulatory T cells with immunosuppressive functions, thereby demonstrating remarkable immunosuppressive efficacy and exerting a protective effect [13]. In recent years, there have been reports of several MND with potential immune-related mechanisms. Some patients have experienced partial relief of clinical symptoms following immunotherapy, suggesting that these MND may have an immune component and fall under the category of immune-related MND syndrome. This syndrome encompasses a group of disorders that exhibit similar clinical features, electrophysiology, and neuroimaging characteristics as MND, along with abnormal immune markers [14]. The concept of immune-related MND syndrome is gaining attention, but a standardized diagnostic criteria or expert consensus is currently lacking, leading to challenges in clinical diagnosis and increasing the risk of misdiagnosis or delayed treatment. This underscores the importance of establishing clear diagnostic guidelines and treatment protocols for immune-related MND syndrome.

SS is a disease characterized by non-organ-specific inflammation related to immunity. A systematic investigation by Seeliger et al. on 184 patients with polyneuropathy and limb weakness found that 24% (44/184) were diagnosed with SS, indicating a frequent association between severe neuropathy with limb weakness and SS [15]. The incidence rates of ALS combined with SS reported in different studies vary significantly, likely due to factors such as lack of standardized inclusion and exclusion criteria, bias in the study population selection, and regional differences [16]. SS can lead to abnormalities in salivary gland function, with the main mechanism being autoimmune-mediated lymphocyte infiltration. Additionally, 20% of ALS cases present with salivation

Table 3 Motor nerve conduction studies

Nerve	Latency (ms)	Amplitude (mV)	Distance (mm)	Conduction velocity (m/s)
Common peroneal nerve (R)				
Ankle	3.85	3.4		
Fib head	14.38 (reference range: <5.5)	3.9 (reference range: >3.0)	310 (reference range: 8 cm)	29 (reference range: >40)
Tibial nerve (R)				
Ankle	6.67	6.3		
Pop fossa	16.25 (reference range: <6.0)	5.5 (reference range: >3.0)	395 (reference range: 10 cm)	41 (reference range: >40)
Deep peroneal nerve (fibular side) (R)				
Fib Head2	4.64 (reference range: <5.5)	5.6 (reference range: >3.0)	120 (reference range: 8 cm)	33 (reference range: >40)
Tibial nerve gastrocnemius branch (R)				
Pop fossa2	4.64 (reference range: <6.0)	20.1 (reference range: >3.0)	151 (reference range: 10 cm)	41 (reference range: >40)
Femoral nerve (R)				
B.Ing Lig	6.56 (reference range: <6.0)	10.8 (reference range: >3.0)	305 (reference range: 10 cm)	55 (reference range: >40)
Common peroneal nerve (L)				
Ankle	4.58	4.8		
Pop fossa	12.5	4.1	295	37
Tibial nerve (L)				
Ankle	5.78	5.3		
Pop fossa	15.52	4.4	395	41
Deep peroneal nerve (fibular side) (L)				
Fib Head1	0.99	3.9		
Fib Head2	4.9	3.1	130	33
Median nerve (L)				
Wrist	5.78	6.2		
Elbow	9.38 (reference range: <4.2)	6.5 (reference range: >5)	190 (reference range: 8 cm)	53 (reference range: >45)
Axilla	11.93	6.6	160	63
Ulnar nerve (L)				
Wrist	4.27	2.4		
A.Elbow	6.46 (reference range: <3.0)	1.9 (reference range: >5)	150 (reference range: 8 cm)	69 (reference range: >45)
B.Elbow	9.48	2.4	112	37
Axilla	11.61	2.7	100	47
Musculocutaneous nerve (L)				
Erb's 1	0.99	4.2		
Erb's 2	5.16 (reference range: 3.9 ± 0.5)	4.5 (reference range: >5)	260 (reference range: 14.8–26.5)	62 (reference range: >60)

L: left; R: right

symptoms, and salivary gland function tests often show abnormalities [17]. However, the mechanism underlying the combination of SS and ALS remains ambiguous. Hypotheses such as ischemic injury, mononuclear cell infiltration, immune-mediated vascular injury of the central nervous system, the impact of anti-neuronal antibodies, or the direct injury effect of SSA on nerve cells are insufficient to fully elucidate ALS symptoms. Currently, SS and other connective tissue diseases have not been definitively categorized as the etiological cause of ALS [18]. Research suggests that patients with a history of multiple sclerosis, myasthenia gravis, polymyositis, SS, and systemic lupus erythematosus have a higher risk of MND compared to the general population one year prior to MND diagnosis [19]. While the coexistence of SS and ALS necessitates further comprehensive investigation for clarification, numerous studies have indicated that immune abnormalities play a significant role in the pathogenesis of ALS. Therefore, the concurrent presence of these conditions is not coincidental. It is theorized that potential mechanisms of the combination of SS and ALS involve T lymphocyte and dendritic cell-mediated vasculitis, dorsal root ganglion injury, and the production of specific antibodies by B lymphocytes reacting with nerve tissue antigens. Nonetheless, additional pathogenic mechanisms await discovery.

In 1999, Katz et al. reported two cases of multi-system neuronal involvement associated with SS. One case presented lower motor neuron syndrome, while the other exhibited upper motor neuron syndrome and sensory neuropathy. Both patients experienced symptom relief after receiving high-dose corticosteroid treatment [20]. Furthermore, a patient with lower motor neuron disease and overlapping syndrome (rheumatoid arthritis, systemic lupus erythematosus, and SS) showed significant improvement in symptoms and laboratory indicators following a three-month treatment regimen of cyclophosphamide, corticosteroids, hydroxychloroquine, and intravenous immunoglobulin (IVIG) [21]. Another patient with SS and lower motor neuron disease did not respond well to corticosteroids; however, plasma exchange (PE) and IVIG led to recovery, with effects lasting around three months [22]. Studies suggest that TNF inhibitors (infliximab and etanercept) and B-cell targeted drugs (rituximab and epratuzumab) could be considered for SS patients with MND [23]; although further large-scale studies are needed for evidence-based support. However, Hagiwara et al. reported two cases of ALS patients with predominant upper motor neuron damage and concurrent subclinical SS. In one case, symptoms did not improve after methylprednisolone treatment but showed significant improvement following IVIG treatment; however, re-treatment with IVIG one month later did not yield favorable outcomes. In the other case, the patient experienced minimal and short-term benefits from hormone treatment, and the condition continued to progress despite plasma exchange and cyclophosphamide therapy. Switching to IVIG treatment led to significant enhancement of symptoms, yet re-treatment with IVIG one month later did not provide benefits [24]. Similarly, in SS patients with rapidly progressive MND who received high-dose corticosteroids, IVIG, and immunosuppressants, symptoms remained unresolved, resulting in respiratory failure and death two months after diagnosis [8]. A patient with SS and lower motor neuron disease, neurogenic bladder, and respiratory failure did not benefit from glucocorticoid treatment [25]. In conclusion, substantial variations exist in treatment regimens and efficacy among SS patients with different types of MND. For rapidly progressive MND or MND patients with multiple comorbidities, the therapeutic outcome is extremely poor, highlighting the importance of early disease identification. Some studies have suggested that corneal confocal microscopy [26] and neurofilament light chain protein [27] may play a role in diagnosing and evaluating the effectiveness of immunotherapy, but further research is needed to fully understand their potential. While SS may worsen motor neuronopathy, some patients do not respond to immunomodulatory treatment, indicating that SS and ALS in the same patient may be coincidentally discovered as independent disorders. Therefore, the potential causal relationship between the two conditions requires additional investigation.

In this case, the patient is a middle-aged male, and his clinical traits are delineated as follows: (1) The onset is insidious, the disease course is chronic, and the symptoms progress gradually. (2) The principal manifestation lies in the concurrent engagement of both upper and lower motor neurons. (3) Associated with numbness and burning sensations in both feet; nonetheless, there is no reduction in pain and prickle sensation, and the electrophysiological examination indicates combined multiple peripheral nerve impairment. (4) The electrophysiological examination reveals neurogenic damage in both upper and lower extremities. (5) Based on the electrophysiological and imaging results of the injury to the upper and lower motor neurons, other diseases can be excluded, and the diagnosis is ALS. Additionally, the patient exhibits symptoms like dry mouth, bitter mouth, and tooth loss. Positive tests for SSA antibody, RO-52 antibody, and antinuclear antibody, along with chronic inflammatory changes seen in lip gland biopsy, lead to a diagnosis of SS by the rheumatologist. In this patient, the onset of neurological symptoms preceded the symptoms of SS in this patient, consistent with previous findings. While ALS has traditionally been considered a neurodegenerative disease affecting only motor neurons, recent evidence suggests potential involvement of other nervous

or non-nervous systems [6]. Globally, 20-30% of ALS patients present with sensory abnormalities, but these are rarely detected in sensory examinations [28]. Hammad et al. studied 103 ALS patients and found that 32% exhibited various sensory abnormalities, with numbness being the most common, followed by neuropathic pain, prickling sensation, and decreased temperature sensitivity [28]. Neurological physical examinations revealed abnormal findings in 20% of patients, including decreased vibration and pinprick perception, impaired warm sensation, and reduced joint position perception [29]. Liu et al. noted that sensory disorders in ALS patients are usually mild and show minimal progression [30]. However, Nolano et al. observed that peripheral sensory involvement worsens in parallel with motor dysfunction in a study of 149 ALS patients [31]. This patient presented with numbness and a burning sensation in both feet, without signs of sensory disorders. The electrophysiological examination indicated multiple peripheral nerve damage, aligning with previous research findings. Given the patient's SS condition, sensory nerve damage is also a potential factor. Therefore, it is crucial to consider the possibility of concurrent sensory abnormalities in ALS patients during diagnosis and treatment. Diagnosis of ALS should not be hastily dismissed based solely on sensory symptoms or electromyogram results, to avoid delays in treatment. Additional diagnostic tools such as small nerve fiber pathology, sensory nerve conduction studies, somatosensory evoked potentials, and laser evoked potentials can be utilized to assess sensory pathway changes in ALS and potentially predict patient survival time [32]. It is essential to admit that in situations where subjective symptoms are not consistent with objective examinations, there is a continuous need for caution regarding the possible existence of autonomic nerve dysfunction. In clinical practice, the condition is usually analyzed based on the symptoms and signs observed in the patient. However, in cases where only symptoms are present, without any associated signs, there is a considerable risk of these cases being neglected. As research advances, it has been discovered that over 80% of ALS patients exhibit at least one non-motor symptom [33]. It is estimated that approximately 75% of individuals with amyotrophic lateral sclerosis (ALS) experience autonomic nerve dysfunction, with the majority showing mild symptoms and a minority presenting with moderate symptoms [34]. It has been demonstrated that autonomic nerve dysfunction may occur simultaneously with the gradual development of ALS. The severity of autonomic nerve dysfunction is a crucial factor in predicting the prognosis of ALS patients, having the potential to accelerate the progression of the disease and decrease their survival expectancy [35]. Similarly, autonomic nerve dysfunction is also common in SS [36]. Recently, studies have suggested that vagus nerve stimulation might be an effective approach for alleviating the symptoms of autonomic nerve dysfunction in SS patients. This indicates that the regulation of autonomic nerve function may represent a promising direction for therapeutic intervention in SS [37]. The patient in this case has both of the aforementioned conditions, and the incidence of autonomic nerve dysfunction is likely to be even higher. It is beneficial to enhance the quality of life and optimize the prognosis of patients with autonomic nerve dysfunction by strengthening the assessment of autonomic nerve function and implementing intervention as early as possible. Previous literature indicates that all reported cases of SS and NMD involved female patients, making this instance the first documented case in a male patient. This highlights the importance of considering immune factors in male NMD patients. Alongside motor symptoms, this patient also experiences severe sleep disorders. Following the exclusion of other potential factors, administering eszopiclone to improve sleep quality and duration has shown positive results. Research indicates that 49 −59% of ALS patients exhibit symptoms of sleep disorders, with causes ranging from respiratory issues and sensory abnormalities to emotional disorders and restless legs syndrome [38].Moreover, sleep disorders signify a presentation of autonomic nerve dysfunction, thereby highlighting the critical significance of evaluating the functions of diverse autonomic nerve domains. The gastrointestinal symptoms (e.g., constipation and abdominal distension), urinary system symptoms (e.g., urgency, urinary incontinence, and urinary retention), and cardiovascular system symptoms (e.g., increased heart rate) manifested by the patient in this case were all non-typical. Consequently, systematic autonomic nerve function screenings, such as urodynamics and heart rate variability, were not carried out. However, considering the coexistence of two autonomic nerve dysfunction symptoms (abnormal sensation and sleep disorder) during the disease course, active intervention measures were adopted. In the subsequent clinical diagnosis and treatment process, it is essential to determine whether the patient exhibits symptoms suggesting autonomic nerve dysfunction. A comprehensive assessment of autonomic nerve function is indispensable, and timely intervention is recommended to improve the prognosis of these patients from multiple perspectives. Despite treatments such as hormones, immunosuppressants, acupuncture, and nerve rehabilitation, the patient's symptoms did not show significant improvement but did not progress rapidly either.

Conclusion

Currently, treatment options for ALS are limited. Actively addressing the concomitant treatable conditions is highly beneficial for optimizing the symptom manifestation and

quality of life of patients. The European League Against Rheumatism (EULAR) SS Disease Activity Index can be used to assess the activity level of SS disease in ALS patients. Additional tests such as autoantibody profiles, dry eye-related tests, and labial gland biopsy may be necessary for further SS screening [39]. Further research is needed to better understand the relationship between autoimmune ALS and SS and to develop more effective treatment strategies beyond immunomodulatory therapy.

Abbreviations

ALS	Amyotrophic lateral sclerosis
MND	Motor neuron disease
SS	Sjögren's syndrome
ANA	Antinuclear antibody
IVIG	Intravenous immunoglobulin
PE	Plasma exchange

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Not applicable.

Author contributions
All authors contributed to the study conception and design. Y.H.L.: patient management, initial draft manuscript preparation, X.P.Z.: concept and design of the study, H.J.L.: literature review, Z.C.X.: pathology analysis; P.X.: radiological profile analysis, final approval of the version to be published. All authors read and approved the final manuscript of "Amyotrophic Lateral Sclerosis Associated with Sjögren's syndrome: A Case Report".

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study is approved by ethics committee of Affiliated Hospital of Zunyi Medical University.

Consent for publication
Written informed consent was obtained from the patient and his family for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Competing interests
The authors declare no competing interests.

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