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Ethical approval: The authors are accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were following the ethical standards of the institutional and/or national research committee(s) and were in conformity with the work and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were following the ethical standards of the institutional and/or national research committee(s) and were in conformity with the Helsinki Declaration. Approved by the Innova Medical Center Ethics Committee (IMC-ALS-2020-0515). The study ensured the privacy and confidentiality of all patient information. The procedures followed were in accordance with

Autologous Mesenchymal Stem Cell Transplantation in Amyotrophic Lateral Sclerosis: A Case Report

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ABSTRACT

INTRODUCTION AND IMPORTANCE

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease with limited treatment options, leading to severe motor impairment and premature death. Current therapies provide only marginal benefits, necessitating novel approaches. Mesenchymal stem cells (MSCs) have gained interest due to their immunomodulatory, neuroprotective, and regenerative potential.

CASE PRESENTATION

This study assesses the safety and therapeutic potential of MSC transplantation in a 52-year-old ALS patient, evaluating functional changes and disease progression. The patient underwent two MSC transplantations via intrathecal and intravenous administration. Clinical evaluations, electromyography (EMG), and ALS Functional Rating Scale-Revised (ALSF-R) assessments were conducted over 5 months post-treatment.

CLINICAL DISCUSSION

Motor function improved post-transplantation, with increased limb mobility and better swallowing. The ALSFRS-R score, which typically declines in ALS, showed a 15% increase, suggesting possible stabilization. EMG revealed preserved sensory fibers despite ongoing motor neuron degeneration. No severe adverse effects were observed.

CONCLUSION

These findings suggest that MSC may have a disease-modifying effect in ALS, offering both functional and emotional benefits. However, this case report has inherent limitations, including the lack of a control group and a small sample size. Key learning points include the safety and tolerability of MSC, its potential to improve motor and bulbar function, and the importance of combining MSC with physical and neurorehabilitation therapies. Future research should focus on larger, controlled trials to confirm efficacy, optimize treatment protocols, and identify patient subgroups most likely to benefit. This case highlights the potential of MSC as a promising therapeutic approach for ALS, warranting further investigation.

Keywords: Amyotrophic lateral sclerosis, Mesenchymal stem cell transplantation, Neurodegenerative disease, Regenerative medicine, Disease-modifying therapy

Introduction

Amyotrophic lateral sclerosis (ALS), commonly referred to as Lou Gehrig's disease, is a debilitating neurodegenerative disorder that results in progressive weakness and eventual death due to respiratory failure.¹ Recent population-based studies have shown a rise in incidence, with a prevalence of 4.1–4.8 per 100,000 individuals and a median onset age of 60–68 years.^{2–6} Despite the

phenotypic variability of ALS, the median survival time from onset to death ranges from 20 to 48 months, with 10–20% of patients living more than 10 years.⁷

At present, only symptom-based and disease-modifying treatments are available, such as Riluzole and Edaravone, which have been FDA-approved but only extend patients' life expectancy by a few months.⁸ In recent years, research has highlighted the role of immune processes, particularly inflammation, in the pathogenesis of ALS.⁹

Mesenchymal stem cells (MSCs) have unique immune properties, expressing various anti-inflammatory and growth factors and exhibiting both immunosuppressive and tissue regeneration abilities.¹⁰ These characteristics make MSCs a promising therapeutic option for treating ALS and mitigating the impact of its debilitating symptoms. Given the neuroinflammatory basis of ALS, MSCs offer a targeted approach by modulating immune responses and promoting neuronal survival. Previous trials, such as Mazzini et al.,²¹ also demonstrated the potential benefits of MSC transplantation in ALS.

In addition to their regenerative potential, MSCs have been shown to retain their functional properties after extensive in vitro expansion, with no evidence of chromosomal aberrations, cellular senescence, or contamination, ensuring their safety for transplantation.¹¹ Moreover, previous research has indicated that ALS itself does not impair MSC proliferation or differentiation capacity, supporting its viability as a therapeutic tool.¹¹

The method of MSC delivery plays a crucial role in optimizing therapeutic outcomes. While systemic administration faces challenges in targeting affected neuronal regions, direct intraspinal implantation has shown promise in ALS animal models.^{12–16}

As ALS clinical research advances, refining MSC-based strategies by optimizing dosing, refining transplantation techniques, and integrating advanced neuroimaging tools will be essential for translating these findings into effective therapeutic interventions. Our study lays the groundwork for future clinical trials exploring MSC transplantation in ALS patients, focusing on improving patient outcomes and quality of life.

Case Description

A 52-year-old female patient was diagnosed with ALS approximately 3 years prior to the present case report. The patient was unable to express her symptoms verbally. Therefore, anamnesis was collected from family, caregivers, and medical records.

The onset of the disease was marked by weakness in the right upper limb, which was the initial symptom. This weakness gradually spreads to other limbs, resulting in movement difficulties. The patient later

existing local and international guidelines and regulations.

Consent: The patient provided informed consent for the publication of her case details, and all procedures were carried out in compliance with ethical standards.

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Author contribution:

Konstantine Chutkerashvili – Conceptualization, Investigation, Methodology, Project administration, Resources

Giorgi Svanishvili – Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing

Lela Mtchedlishvili, Mariam Maisuradze, Ekaterine Mikeltadze – Investigation, Writing – original draft, Writing – review & editing

Guarantor: Giorgi Svanishvili

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experienced speech and swallowing difficulties, dyspnea, and signs of drooling. She had no known family history of ALS and was not exposed to any known risk factors, such as smoking or heavy metal exposure. A previous head injury sustained in a car accident 30 years before the diagnosis was reported, but it is not believed to have contributed to the development of ALS.

Genetic screening for motor neuron disease was performed and revealed a heterozygous nucleotide change in the UBQLN2 gene, which had no significant clinical correlation. Also, genetic screening for motor neuron disease (SOD1, FUS, C9ORF72, TARDBP, PPN1, VCP, OPTN, and SQSTM1) revealed no mutations. Electromyography exams performed in 2018 showed generalized motor neuron dysfunction, and the patient was prescribed Riluzole. Edaravone treatment was later initiated but discontinued due to its ineffectiveness. The patient required noninvasive ventilation and suctioning to maintain an upright position and manage drooling.

The patient was diagnosed with ALS based on her clinical presentation and examination results. To manage her symptoms, she underwent two rounds of MSC transplantation at Innova Medical Center in Tbilisi on May 15 and July 10, 2020. Neurologic exams performed after the transplantation showed left-sided facial asymmetry due to a lower branch central palsy of the seventh cranial nerve, deep tetraparesis, periodic coughing, and diffuse tongue fasciculations. The patient had difficulty lifting her legs, and fibrillations were observed after muscle irritation. A bilaterally

positive Babinski's sign was present, and pelvic organ functions were controlled.

This case report highlights the phenotypic variability and progressive nature of ALS, as well as the limited options for treatment currently available. Despite these challenges, the patient's response to MSC transplantation serves as a promising avenue for further research into potential therapies for this devastating disease.

Methods

Bone marrow (100 ml) was collected from the anterior superior iliac spine under local anesthesia using a sterile technique. The aspirated bone marrow was transferred to a sterile test tube with heparin and diluted with a phosphate buffer solution at a 1:2 ratio. To isolate the mononuclear cell fraction, we performed density gradient centrifugation using Ficoll-Paque Plus or Ficoll-Paque Premium solution (GE Healthcare, USA) at 400 xg for 30 minutes at room temperature. This process yielded approximately 750 million mononuclear cells.

Cell viability was assessed by examining 0.4 ml of the sample with a trypan blue exclusion test and cytometric analysis, following a standardized protocol with 0.4% trypan blue solution (Sigma, USA). For immunophenotyping, the mononuclear cell fraction was stained with 0.5% BSA/PBS and antibodies, including anti-human CD34, anti-human CD45, anti-human CD271 (Miltenyi Biotec, Germany), and anti-human STRO-1 (Santa Cruz Biotechnology, USA). Flow cytometry was conducted using a BD FACSCalibur machine (Becton Dickinson, USA).

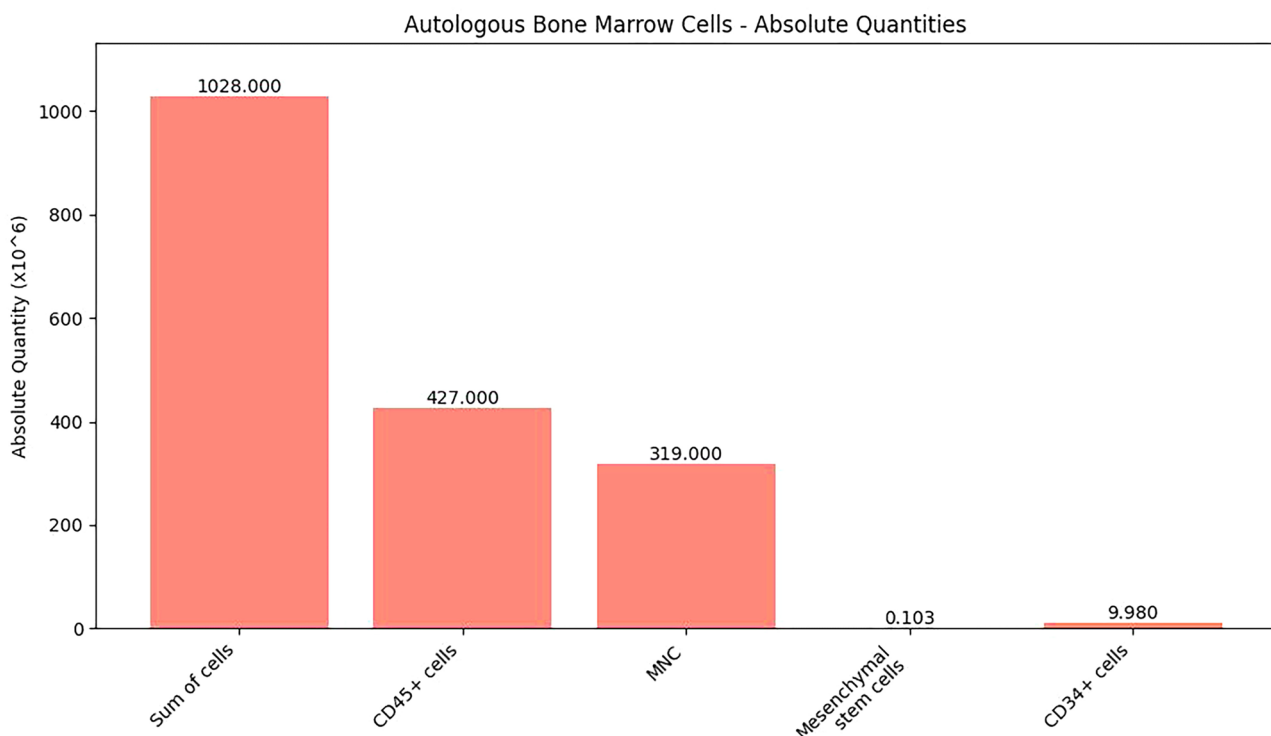


Fig 1 | Absolute quantities of autologous bone marrow cell fractions. The chart presents the absolute quantities (in millions) for key cell fractions—including total cells, CD45+ cells, MNC, MSCs, and CD34+ cells—derived from the bone marrow sample. The visualization provides a quantitative assessment of the cellular composition, which is critical for evaluating sample quality and potential therapeutic efficacy.

Immunophenotyping results identified bone marrow MSCs as CD45⁻, CD34⁻, CD271⁺, and STRO-1⁺ cells, with their absolute numbers calculated accurately. We also confirmed the presence of hematopoietic stem cells (CD45⁺/CD34⁺) within the mononuclear cell population. The total counts of autologous bone marrow cells and stem cells are shown in Figure 1.

The first MSC administration occurred on May 15, 2020, via intrathecal injection through a lumbar puncture between the L3 and L4 vertebrae under local anesthesia. The second administration combined intrathecal and intravenous routes, delivering 750 million cells per transplantation. Post-procedure, the patient was monitored closely and discharged 24 hours later.

To evaluate patient progress, we used a neurologic examination, the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R), and electromyography (EMG). The ALSFRS-R, a validated 12-item tool, tracks disease progression and patient status.¹⁷ Following the May 15, 2020 transplantation, the patient underwent periodic evaluations over 5 months, including neurologic exams, ALSFRS-R assessments, and EMG. Muscle manual test results are presented in Figure 2.

This case report was conducted in accordance with the CARE (Case REport) guidelines,¹⁸ which provide a standardized framework for reporting clinical cases to ensure transparency, accuracy, and completeness. The patient provided informed consent for the publication of her case details, and all procedures were carried out in compliance with ethical standards.

Discussion

This case report describes a 51-year-old female patient with ALS who underwent two stem cell transplantations, spaced 2 months apart and was monitored over 5 months (May 15, 2020, to September 10, 2020). The

patient's progress was evaluated using the ALSFRS-R and EMG, with both subjective and objective improvements observed. Notably, the patient's ALSFRS-R score increased by 15%, rising from 13 to 19 points over 5 months (Figure 3), in contrast to the typical 17% decline seen in ALS patients every 6 months.¹⁸ This suggests a potential stabilization or even improvement in function, which is highly encouraging given the progressive nature of ALS.

One month post-transplantation, the patient demonstrated significant improvements in motor function, including the ability to lift her leg over the bed to a 10–20-degree angle and independently cross her tibias. By the second month, this progressed further, with her leg lift reaching a 20–30-degree angle. These gains in lower limb strength were accompanied by improvements in bulbar function, as evidenced by her ability to chew and swallow solid food, although she still struggled with handling utensils. Speech clarity and swallowing also improved, as reflected in the ALSFRS-R scores, and she no longer required suction, non-invasive positive pressure ventilation (NIPPV), or other forms of oxygen support. These findings highlight the potential of stem cell transplantation to address both motor and bulbar symptoms in ALS.

EMG results from 2 months post-transplantation revealed preserved sensory fibers but indicated axonal degeneration in motor fibers. Denervation was observed in both upper and lower limb muscles, as well as chronic denervation in the tongue muscles. The increased spontaneous activity in the tongue muscles aligns with the typical progression of ALS, where bulbar muscles are often affected later in the disease course. Despite these findings, the patient's overall functional improvements suggest that stem cell

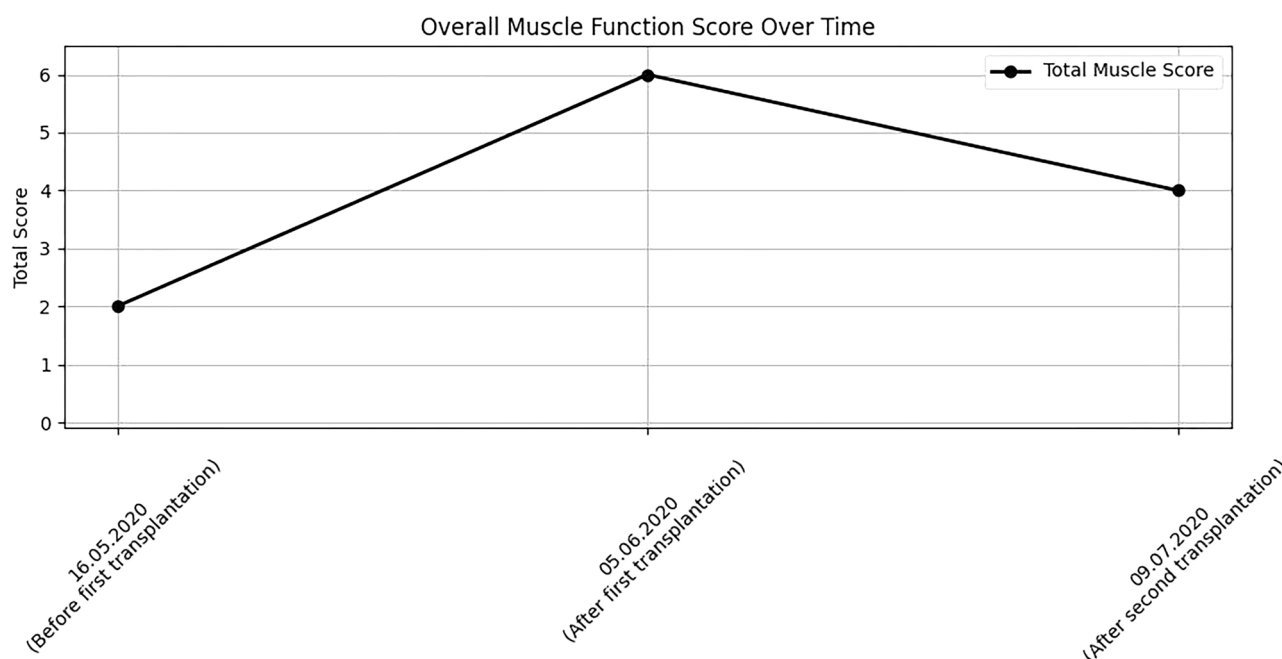


Fig 2 | Dynamic changes in muscle manual test scores. This figure illustrates the evolution of muscle function in seven distinct muscle groups assessed at three time points surrounding transplantation procedures.

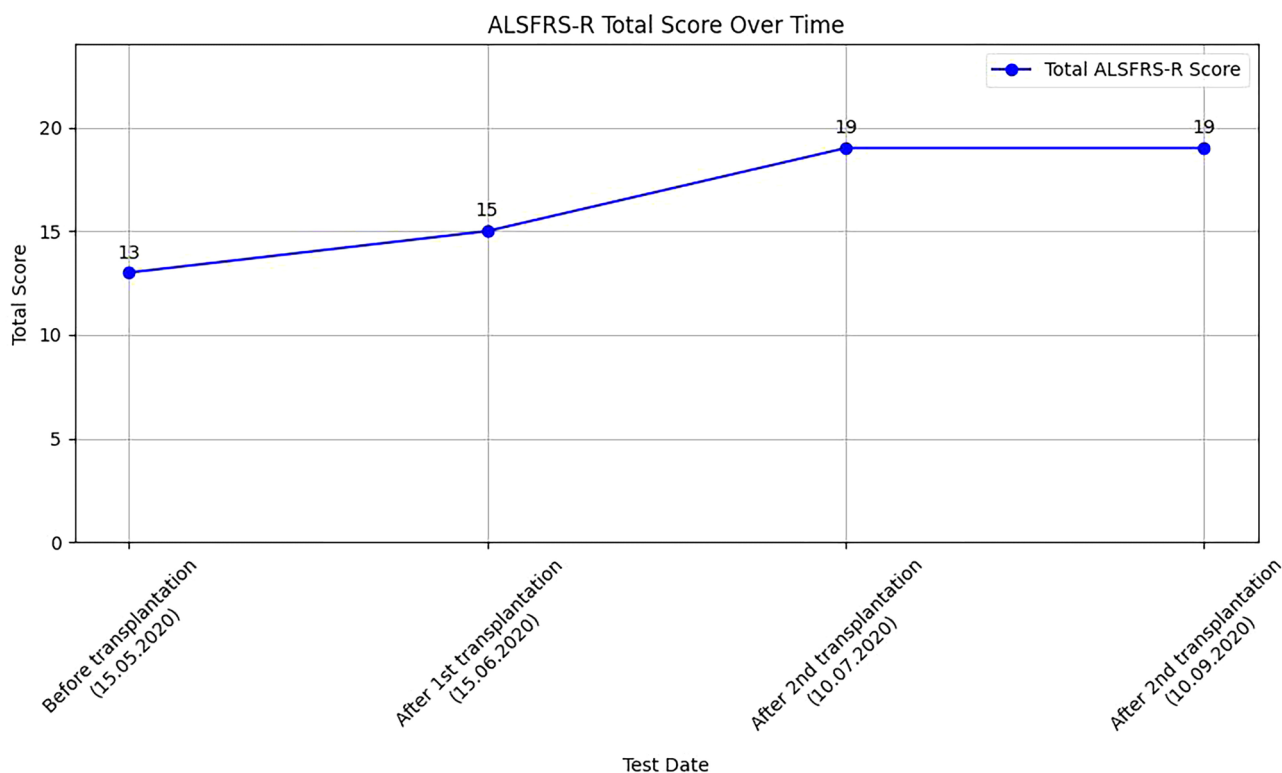


Fig 3 | ALSFRS-R total score dynamics following transplantation. The line graph displays changes in the ALSFRS-R total score measured at four distinct time points: before transplantation, after the first transplantation, and at two post-second transplantation assessments. This progressive trend highlights functional changes over time, suggesting potential stabilization or improvement in the patient's neurological status following treatment.

transplantation may have contributed to neuroprotection or partial restoration of motor function.

The patient's emotional state also showed significant improvement following treatment. Prior to the intervention, she exhibited signs of depression, stress, and hopelessness, which are known to negatively impact ALS prognosis.¹⁹ However, caregivers reported a marked increase in her engagement, optimism, and energy levels after the transplantations. This improvement in emotional well-being is consistent with the expected outcomes of the treatment protocol and underscores the holistic benefits of the intervention.

The stem cell transplantations were administered via intrathecal and intravenous routes, with no significant adverse effects observed apart from transient symptoms such as headaches and local rigidity. The intrathecal route was chosen for its precision in delivering cells to the affected areas and its favorable safety profile.²⁰ MSCs are known for their immunomodulatory properties, plasticity, and ability to secrete growth factors and cytokines that promote tissue repair.²¹ Additionally, MSCs interact with immune cells and create a neuroprotective environment,²² which may explain the observed improvements in this patient.

Following the stem cell therapy, the patient was prescribed physical therapy to maintain and improve muscle strength, coordination, and endurance. Neurorehabilitation therapy was also recommended, as it can enhance the effects of MSCs by promoting their mobilization and supporting angiogenesis.²³ These adjunct therapies likely contributed to the observed

improvements in the patient's condition. Over the 5-month monitoring period, no signs of health deterioration were observed, and the disease progression appeared to slow significantly.

The patient had no significant risk factors for ALS, aside from a single episode of head trauma sustained in a car accident 30 years prior. However, the link between isolated head trauma and ALS remains unsupported in the literature.²⁴ Prior to treatment, the patient exhibited signs of respiratory insufficiency, a poor prognostic indicator in ALS,²⁵ as well as dysphagia and excessive drooling. These factors, combined with her initial emotional state of sadness and hopelessness, underscored the urgency of intervention.

This case highlights the safety and potential efficacy of stem cell transplantation in ALS treatment, offering both functional improvements and a positive impact on the patient's emotional well-being. While further research is needed to validate these findings, the results are promising and warrant continued investigation into the use of MSCs for ALS treatment. The combination of stem cell therapy with physical and neurorehabilitation therapies may provide a comprehensive approach to managing this debilitating disease.

Limitation

The limitations of this case report include a lack of blind evaluation, limited electromyography data due to tetraparesis, and generalized muscle atrophy. As the patient's speech was impaired, the medical history was gathered from family members, caregivers, and

physicians. The patient underwent plasmapheresis after the second transplantation, which could have affected the progression of the disease. However, the observed improvement and slowing of disease progression suggest the potential benefits of MSC transplantation.

Conclusion

The results of this study suggest that mesenchymal stem cell transplantation (MSCT) is a safe and potentially effective treatment for ALS. The patient demonstrated improvements in motor, bulbar, and respiratory functions, as well as enhanced emotional well-being, which may be attributed to the regenerative, neuroprotective, and immunomodulatory properties of MSCs. These findings align with existing evidence supporting the therapeutic potential of MSCs in neurodegenerative diseases and provide further insight into their ability to modify disease progression in ALS.

MSCT was well-tolerated, with no significant adverse effects beyond transient symptoms such as headaches and local rigidity. This reinforces the safety profile of intrathecal and intravenous MSC administration in ALS patients. However, potential risks, such as immune reactions or unintended differentiation of MSCs, cannot be ruled out and warrant careful monitoring in future studies.

While these results are promising, this case report has inherent limitations, including the lack of a control group and the small sample size ($n = 1$). Therefore, the findings should be interpreted as preliminary. Future research should focus on larger, multi-center controlled trials to confirm the efficacy of MSCT in ALS. Key areas for investigation include optimizing MSC dosage, administration routes (e.g., intrathecal vs. intravenous), and treatment frequency, as well as identifying patient subgroups most likely to benefit from this therapy.

In conclusion, this case report highlights the potential of MSCT as a promising therapeutic approach for ALS. While further research is needed to validate these findings and address remaining questions, the results provide a strong foundation for future studies and underscore the importance of continued investigation into the safety, efficacy, and optimization of MSCT for this devastating disease.

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Supplementary Material**Table S1 | Autologous bone marrow cells fraction percentages and absolute quantities**

	Percentage (%)	Absolute Quantity
Sum of the cells in the sample	100	1028×10^6
CD45 positive cells fraction	41.5	427×10^6
Mononuclear cells fraction (MNC)	31	319×10^6
Mesenchymal stem cells fraction CD45-/CD105+/CD90+	0.01	103×10^3
CD34+ cells fraction (hematopoietic stem cells)	0.97	9.98×10^6

Table S2 | Muscle manual test

	16.05.2020 (Before First Transplantation)	05.06.2020 (After First Transplantation)	09.07.2020 (After Second Transplantation)
Deltoid muscles	1	1	1
Biceps muscles	0	1	0
Triceps muscles	0	1	0
Muscles of finger flexion	1	1	1
Hip flexion-extension	0	1	1
Shin flexion-extension	0	1	1
Foot flexion-extension	0	0	0

0: no visible or palpable contraction; 1: visible or palpable contraction with no motion; 2: full ROM (range of motion) gravity eliminated; 3: full ROM against gravity; 4: full ROM against gravity, moderate resistance; 5: full ROM against gravity, maximal resistance

Table S3 | ALSFRS-R (amyotrophic lateral sclerosis functional rating scale - revised)

	Before Transplantation (15.05.2020)	After First Transplantation (15.06.2020)	After Second Transplantation (10.07.2020)	After Second Transplantation (10.09.2020)
Speech	1	1	2	2
4 – Normal Speech processes				
3 – Detectable speech with disturbances				
2 – Intelligible with repeating				
1 – Speech combined with non-vocal communication				
0 – Loss of useful speech				
Salivation	0	1	2	2
4 – Normal				
3 – Slight but definite excess of saliva in mouth; may have nighttime drooling				
2 – Moderately excessive saliva; may have minimal drooling				
1 – Marked excess of saliva with some drooling				
0 – Marked drooling; requires constant tissue or handkerchief				
Swallowing	2	3	3	3
4 – Normal eating habits				
3 – Early eating problems – occasional choking				
2 – Dietary consistency changes				
1 – Needs supplemental tube feeding				
0 – NPO (exclusively parenteral or enteral feeding)				
Handwriting	0	0	0	0
4 – Normal				
3 – Slow or sloppy; all words are legible				
2 – Not all words are legible				
1 – Able to grip pen but unable to write				
0 – Unable to grip pen				
Does the subject have a gastrostomy?	No	No	No	No
No – Answer 5a				
Yes – Answer 5b				
a. Cutting Food and Handling Utensils (patients without gastrostomy)	0	0	0	0
4 – Normal				
3 – Somewhat slow and clumsy, but no help needed				
2 – Can cut most foods, although clumsy and slow; some help needed				
1 – Food must be cut by someone, but can still feed slowly				
0 – Needs to be fed				

(Continued)

Table S3 | (Continued)

	Before Transplantation (15.05.2020)	After First Transplantation (15.06.2020)	After Second Transplantation (10.07.2020)	After Second Transplantation (10.09.2020)
b. Cutting Food and Handling Utensils (alternate scale for patients with gastrostomy)	N/A	N/A	N/A	N/A
4 – Normal				
3 – Clumsy but able to perform all manipulations independently				
2 – Some help needed with closures and fasteners				
1 – Provides minimal assistance to caregivers				
0 – Unable to perform any aspect of task				
Dressing and Hygiene	0	0	0	0
4 – Normal function				
3 – Independent and complete self-care with effort or decreased efficiency				
2 – Intermittent assistance or substitute methods				
1 – Needs attendant for self-care				
0 – Total dependence				
Turning in bed and adjusting bed clothes	2	2	2	2
4 – Normal				
3 – Somewhat slow and clumsy, but no help needed				
2 – Can turn alone or adjust sheets, but with great difficulty				
1 – Can initiate, but not turn or adjust sheets alone				
0 – Helpless				
Walking	1	1	2	2
4 – Normal				
3 – Early ambulation difficulties				
2 – Walks with assistance				
1 – Non-ambulatory functional movement only				
0 – No purposeful leg movement				
Climbing Stairs	0	0	0	0
4 – Normal				
3 – Slow				
2 – Mild unsteadiness or fatigue				
1 – Needs assistance				
0 – Cannot do				
R-1-Dyspnea	1	1	1	1
4 – None				
3 – Occurs when walking				
2 – Occurs with one or more of the following: eating, bathing, dressing				
1 – Occurs at rest, difficulty breathing when either sitting or lying				
0 – Significant difficulty, considering using mechanical respiratory support				
R-2 Orthopnea	3	3	3	3
4 – None				
3 – Some difficulty sleeping at night due to shortness of breath, does not routinely use more than two pillows				
2 – Needs extra pillow in order to sleep (more than two)				
1 – Can only sleep sitting up				
0 – Unable to sleep				
R-3 Respiratory Insufficiency	3	3	4	4
4 – None				
3 – Intermittent use of NIPPV				
2 – Continuous use of NIPPV during the night				
1 – Continuous use of NIPPV during the night and day				
0 – Invasive mechanical ventilation by intubation or tracheostomy				
Total	13	15	19	19
Disease duration. How many years?		3		
NIPPV: non-invasive positive pressure ventilation; N/A: not applicable				