European Review for Medical and Pharmacological Sciences 2021; 25: 4086-4090

Long-term survival of a patient with amyotrophic lateral sclerosis (ALS) who received autologous adipose-derived mesenchymal stem cells

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Abstract. – OBJECTIVE: Amyotrophic lateral sclerosis (ALS) is a progressive debilitating neurodegenerative disease with a life expectancy of 3-5 years from initial symptoms. We report a case of ALS who received autologous adipose-derived mesenchymal stem cells (ADSC) and was followed up for 7 years.

CASE REPORT: A 46-year-old man noticed weakness of his legs, difficulties on going down the stairs and coughing during eating in 2009. After complete workout, a diagnosis of ALS was confirmed. His ALS Functional Rating Scale-R (ALSFS-R) was 43. Symptoms rapidly progressed and he coughed and choked during eating. Starting in 2013, the patient received a total of six intravenous infusions of autologous ADSC. Changes in electromyogram, nerve conduction, and ALSFS-R were assessed.

RESULTS: Soon after the administration, he noticed that he did not cough during conversation or eating food. Although he had difficulty in walking down the stairs, he remained well without coughing, dysarthria, or dysphagia. His ALSFS-R increased up to 45. Fascicular potentials were not detected in any muscles examined including trapezius muscle and rectus femoris muscles. The patient was well for 7 years after ADSC therapy by the time of this report and more than 10 years from the time of onset.

CONCLUSIONS: The present case suggests that autologous ADSC can be administered safely and may be potentially useful in patients with ALS. Further investigations are warranted in order for the results to be generalized to other ALS patients.

Key Words:
Amyotrophic lateral sclerosis (ALS), Prognosis, Long survival, Stem cell, Safety.

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder affecting motor neurons, characterized by paralysis and death within 3 to 5 years from the time of diagnosis[1]. The mechanisms underlying ALS in largely unknown, and no effective therapy is currently available. In animal model of ALS, systemic or intra-spinal administration of stem cells from bone marrow or adipose tissues was shown to delay motor neuron degeneration and improve motor function[2,3]. Furthermore, several clinical trials have used mesenchymal stem cells (MSC) for treatment of neurological diseases due to their safety and immunomodulatory and neuroprotective effects[4-7]. The encouraging results of safety and protective effect of MSC provide rationales for investigations on their potential use in ALS patients.

Here, we report a case of ALS who received autologous adipose-derived mesenchymal stem cells (ADSC). The patient survived more than a decade from the onset of disease with neither tube feeding nor intubation.

Case Report

A 46-year-old man noticed weakness of his legs and difficulties on going down the stairs and coughed when he ate in fall 2009. In a year, he developed coughing at conversation and was diagnosed as having asthma. Medication for asthma did not work and the symptoms were slowly progressed. In April 2011, he needed handrail on going down the stairs. He consulted to a neurologist at

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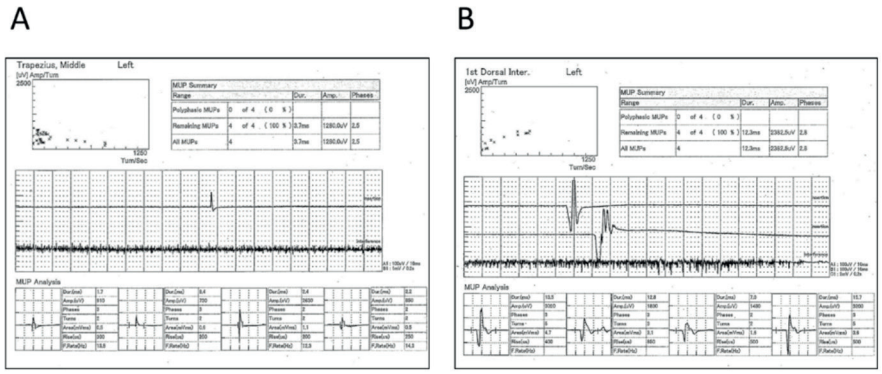


Figure 1. A, EMG 2011-6-9 Trapezius, Middle fasciculation. Fasciculations observed in the trapezius middle muscle on June 9th, 2011. **B,** EMG 2011-6-9 1stDorsal Inter fasciculation. Fasciculations observed in the 1st dorsal interdorsal muscle on June 9th, 2011.

a University Hospital, where his spastic paralysis, dysarthria, and dysphasia were confirmed. His symptoms were continued to be worsening. He noticed fasciculation in his left upper limb and lower limbs in November 2011. He was admitted to the hospital in December 2011. On admission, his walking was unstable, and he was unable to do tandem gait. Gowers' sign was positive. His consciousness level was normal, and his mental functions were not disturbed. He showed neither ataxia nor sensory disturbance. There were no symptoms due to autonomic dysfunction such as orthostatic hypotension except for a moderate constipation.

Neurological examination revealed muscle weakness in limbs predominantly on the right side, elevated muscle stretch reflexes in biceps brachii, triceps brachii, quadriceps, and Achilles' tendons. Orbicularis oculi reflexes, orbicularis oris muscle reflex, and snout reflex were positive. Fasciculations were observed in the trapezius muscle and the left interossei dorsalis muscle. Electromyogram study confirmed fasciculation potentials in the trapezius muscle (Figure 1A), first interdorsal muscle (Figure 1B), and rectus femoris muscles. Nerve conduction velocities as well as the amplitudes, latencies were normal in both motor and sensory nerves. Median nerves and tibial nerves in both sides were examined

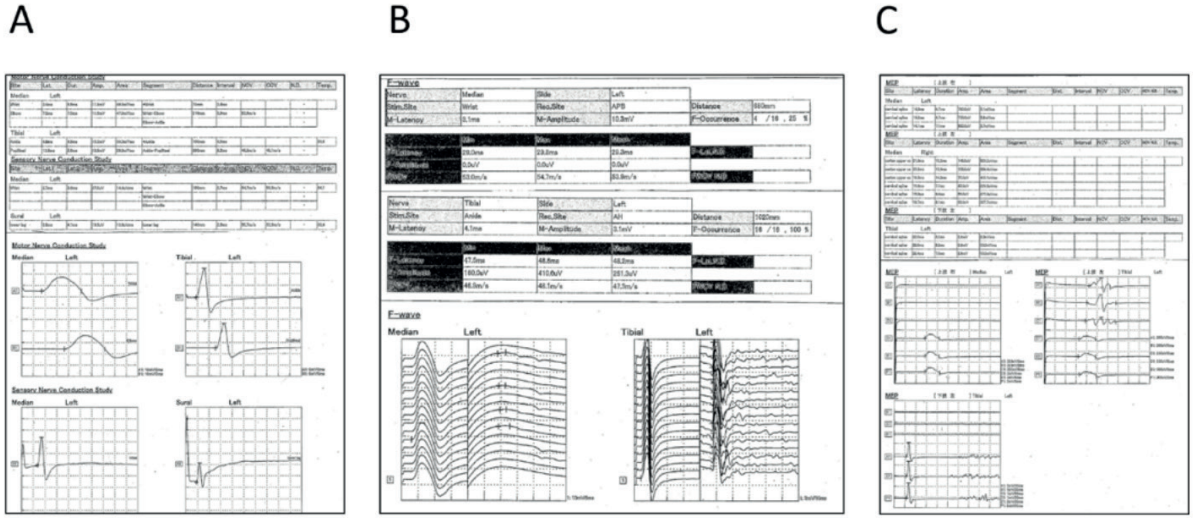
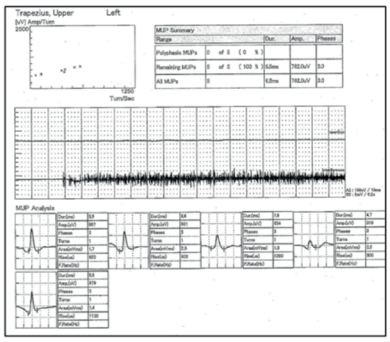


Figure 2. A, Nerve conduction velocities, amplitudes, latencies were normal in both motor and sensory nerves (both sides median nerves and tibial nerves). **B,** The data of F waves, and motor evoked potentials (MEPs). **C,** The data of F waves, and motor evoked potentials (MEPs).

A



B

EMG Findings Summary

Muscle	Side	Ins. Act.	Fibs.	PSWs	FPs	MYD	Amplitude	Phase	Duration	Int.Patt.	Recruit.	CRD
Trapezius, Upper	L	Normal	0	0	0	0	Normal	Mono	Normal	Full	Normal	–
Paraspinal,Thoracic	L	Normal	0	0	0	0	Normal	Mono	Normal	Full	Normal	–
1st Dorsal Inter.	L	Normal	0	0	0	0	Normal	Mono	Normal	Full	Normal	–
Biceps Brachii	L	Normal	0	0	0	0	Normal	Mono	Normal	Full	Normal	–
Vastus Lateralis	L	Normal	0	0	0	0	Normal	Mono	Normal	Full	Normal	–
Tibialis Anterior	L	Normal	0	0	0	0	Normal	Mono	Normal	Full	Normal	–

Figure 3. **A,** EMG in the trapezius muscle on October 1st, 2015. No fasciculation was detected. **B,** Summary of EMG study on October 1st, 2015. EMG study showed no abnormality.

(Figure 2A). The data of F waves, and Motor Evoked Potentials (MEPs) were shown in Figures 2B, 2C. Brain and spinal MRIs showed no abnormality. Serum CPK value was 153 u/l.

He was diagnosed as ALS, and his wife was informed of the disease. There was no family history of ALS. The patient was given riluzole prescription (Sanofi Corp, Tokyo, Japan). ALS Functional Rating Scale-R (ALSFS-R) was 43. Its breakdown was as follows: Speech 3; Salivation 3; Swallowing 3; Handwriting 4; Cutting food 4; Dressing and hygiene 4; Turning in bed 4; Walking 3; Climbing stairs 3; Dyspnea 4; Orthopnea 4; and Respiratory insufficiency 4. He was registered with the Japan Ministry of Health, Labor and Welfare as an ALS case. His symptoms were progressive, and ALSFS-R was 31 in August 2013.

The ADSC treatment was approved by the Ethics Committees of the EBISU Medical Clinic and the Ethics Committees of the Takeda Hospital. It was also approved by the Special Committee for Regenerative Medicine of Kouseikai Takeda Hospital (NA8150024). The stem cell therapy was done according to the guideline of the quality management concerning clinical research of human ADSC. The treatment was approved by the Ministry of Health, Labor and Welfare (PB5160011). The written informed consent from the patient was obtained for the treatments in accordance with the Declaration of Helsinki.

Autologous ADSC were prepared and preserved in liquid nitrogen. in brief, adipose tissue (about 15 g) was obtained from subcutaneous area of patient's abdomen under local anesthesia with 1.0% xylocaine. the tissue was digested using collagenase enzyme. the isolation and characterization of ADSC followed the method as described in detail in our previous publication[8]. The patient had undergone rigorous laboratory examinations for viruses and other pathogens to ensure pathogen-free preparations.

Results

The patient received an intravenous administration of autologous adipose derived stem cells (ADSC) in September 2013 followed by another administration in October 2013. Soon after the administration, he noticed no cough during conversation or eating food. His ALSFS-R in December 2013 was 46. The third administration was done in September 2014. Fascicular potentials were not detected in any muscles examined including trapezius muscle and rectus femoris muscles on October 1, 2015 (Figures 3A, B). Although he had a difficulty in walking down the stairs, he remained well without coughing, dysarthria, and dysphagia for about two years. Thereafter, he noticed that his symptoms were getting worse

again. In March 2017, his ALSFS-R was 32. His grasping power was 38 kg on the right side and 32 kg on the left side, respectively. He received additional ADSC administrations for 3 times (in March, May, and July 2017). In October 2017, his ALSFS-R was 42. He felt much better after the second set of ADSC administrations because he could speak and eat easier. He had no cough and choking anymore. Muscle stretch reflexes were normal. Electromyography and nerve conduction velocity studies revealed no abnormal finding. He could eat without choking or coughing and ALSFS-R was 45 in December 2019. There was no adverse reaction after ADSC administrations. The number of ADSC administrations in each time were 3.8×10^7, 4.2×10^7, 1.7×10^7, 5.9×10^7, 4.3×10^7, and 5.2×10^7, respectively. The patient remained well for 7 years after ADSC therapy by the time of this report and more than 10 years from the onset of the disease.

Discussion

Although there is a case report of ALS patient who had lived for more than a decade[9], it is extremely rare for ALS patients to survive more than a decade with neither tube feeding nor intubation as in our patient. The extreme rarity of this case prompted us to report it, although the underlying reason for the long-term survival still remains unknown. The significance of this case is huge, because ALS is an incurable disease that usually leads to death in about 3 to 5 years. However, our patient remains well for more than 10 years from the first diagnosis.

Our patient was diagnosed as ALS based on electro-diagnostic criteria (Awaji criteria) for diagnosis of ALS[10]. There were clinical and electrophysiological evidence by the presence of lower motor neuron (LMN) as well as upper motor neuron (UMN) signs in the bulbar region and at least two spinal regions, or the presence of LMN and UMN signs in three spinal regions. Rigorous differential diagnoses were performed by electrophysiological examinations, MRIs, and blood tests. In addition, the diagnosis of ALS was confirmed by multiple specialists at multiple hospitals, including a university hospital, which precludes the possibility of misdiagnosis. The patient's diagnosis of ALS was also approved by the Ministry of Health, Labor and Welfare of Japan. Although it is only one case and there is no counterpart control case, we believe that the stem cell therapy might have provided beneficial effects and contributed to the patient's improvement. In fact, several previous studies have also observed such improvements[4-6].

The patient's symptoms rapidly progressed in the first few years, similar to that in the typical ALS. There was no family history of ALS. The patient might have a specific genetic mutation like a heterozygous duplication mutation (c.304_309dupGCCTCG) within exon 1 of the spastin gene[2], but we could not confirm it. Fasciculation is characteristic of ALS, but not necessarily specific for ALS. However, based on clinical symptoms, MRI findings and other neurophysiological findings, it is unlikely that any disease other than ALS could fit this patient's diagnosis. The unexpected events in the course of observing and treating of the patient was that, firstly his progression of symptoms stopped or even resolved in part after ADSC treatment. Secondly, his long-term survival with neither tube feeding nor intubation was a very rare event, thus was worth reporting. The fact that his 2015 re-test showed no abnormalities at all together with improvement in symptoms indicates that the disease improved during the period of ADSC treatment, i.e., between 2011 and 2015.

Although the mechanisms of effects of MSC on ALS remain largely unclear, neurotrophic growth factors and immune modulating factors produced by the MSC may have positive effect on ALS[4]. Previous studies showed that an intrathecal injection of bone marrow-derived mesenchymal stem cells (BMSC) in 19 patients with ALS was clinically feasible and relatively safe procedure and induced immediate immunomodulatory effects[5]. Furthermore, phase 2 clinical trial of intrathecal single administration of BMSC for ALS patients proved its safety and demonstrated promising signs of efficacy[6]. Single or double intrathecal administrations of ADSC in patients with ALS were also safe[7].

The strengths of the ADSC treatment include, 1) Adipose-tissue source which is easier to obtain than bone marrow tissue, 2) Intravenous injection which is easier than intrathecal injection and can be done repeatedly, 3) The safety of ADSC administration which is supported by previous studies[11,12] and also by our patient who received ADSC for 6 times and was followed up to 7 years after the first administration. There was no side effect during and after

the injections. The patient could eat without choking and returned to his work.

Conclusions

We experienced a patient with ALS who survived more than a decade with neither tube feeding nor intubation after the onset of the disease. Repeated intravenous administrations of autologous ADSC were performed without any adverse effect. The patient received no other treatment than the administration of ADSC (there is no drug to prolong life). The fact that his symptoms had improved over time suggests that ADSC treatment might have played some role. The present case suggests that autologous ADSC can be administered safely and may be potentially useful in patients with ALS. Further investigations are warranted in order for the results to be generalized to other ALS patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Consent for Publication

Written informed consent was obtained from the patient for the publication of this case report.

Authors' Contributions

All authors contributed equally to this work, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. KS was a major contributor in writing the manuscript. TT was a major contributor in taking care of the patient. NK analyzed and discussed safety and effect of ADSCs for ALS. NU, KO, and KT prepared and cultured ADSCs. HY conceptualized and designed the ADSCs therapy for ALS. All authors read and approved the final manuscript.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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