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Amyotrophic lateral sclerosis in pregnancy: clinical outcome during the post-partum period after stem cell transplantation into the frontal motor cortex

HECTOR R. MARTÍNEZ[1,2,3], SERGIO SALAZAR MARIONI[3], CÉSAR E. ESCAMILLA OCAÑAS[3], MARÍA TERESA GONZALEZ GARZA[3] & JORGE E. MORENO-CUEVAS[3]

[1]*Instituto de Neurología y Neurocirugía, Centro Médico Zambrano Hellion, San Pedro,* [2]*Servicio de Neurología, Hospital San Jose TEC de Monterrey, Monterrey, and* [3]*Cellular Therapy Department, CITES Medical School Tecnológico de Monterrey, Monterrey, Mexico*

Abstract

Background aims. Amyotrophic lateral sclerosis (ALS) is rare in pregnant patients. Stem cell therapy has been proposed as a potential therapeutic strategy for ALS. *Methods.* We describe a young woman with sporadic ALS that started during the second trimester of pregnancy with a rapid progression after delivery and severe motor impairment. Several drugs and stem cell injection by lumbar puncture were performed without changes before the patient was referred to our institution. *Results.* After bilateral autologous stem cell transplantation into the frontal motor cortices, we observed stabilization in ALS functional rating scale, significant delay of ALS progression and an extension in her life expectancy. *Conclusions.* Stem cell transplantation may alter the clinical course of ALS and improve quality of life in pre-menopausal women.

Key Words: *ALS, pregnancy, stem-cell transplant*

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal progressive neurodegenerative disease. Its clinical features are attributable to the superimposition of motor deficits occurring in the upper motor neurons and lower motor neurons. The onset of ALS is most frequently observed in older adults 55–75 years old (1). Manifestation of ALS is unusual in patients <40 years old; its manifestation in women of childbearing age is an infrequent event (2).

Pregnancy often renders treatment complex. Several different therapeutic options have been employed, mainly pharmaceutical; however, stem cell therapy remains an unexplored method. We describe a patient with ALS who experienced motor symptoms beginning in the second trimester of pregnancy. After a normal delivery, this patient was treated with stem cell transplantation into the frontal motor cortices.

Case report

A 37-year-old primigravida presented with progressive upper left limb weakness that was first noticed at the ninth week of gestation and remained stable during pregnancy. She denied any family history of neuromuscular disorders. She was not taking any medication and denied a recent history of toxin exposure. In March 2011, at 38 weeks' gestation, she delivered by cesarean section a healthy boy weighing 3200 g; Apgar score was 10 at 1 min and 5 min. The child remains healthy and without complications at the present time.

After delivery, clinical impairment progressed; the diagnosis of ALS was established according to El Escorial clinical and neurophysiologic criteria (3). The patient developed cramps in the neck and upper extremities with increased weakness. Neurologic examination revealed 3/5 and 4/5 weakness in the proximal and distal upper limbs, respectively, with a split-hand syndrome; strength in the legs remained normal. Cranial nerve examination was relevant for intermittent tongue fasciculations. Stretch reflexes were normal. Bilateral Hoffmann, left Babinski and Chaddock signs were detected. Sensory tests with pin, cold, vibration, and proprioception were also normal.

Correspondence: **Hector R. Martinez**, MD, PhD, Batallon de San Patricio, No. 112 Colonia Residencial, San Agustin, San Pedro Garza Garcia, NL, Mexico.
E-mail: hector.ramon@itesm.mx

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Over the following 2 months, the patient's clinical condition deteriorated rapidly. Weakness increased 1/5 and 3/5 in the left and right upper limbs, respectively, and 4/5 in the lower extremities. Tongue atrophy, fasciculations and increase in salivation became evident; speech and deglutition were spared. She reported difficulties in walking, climbing stairs, and increasing clumsiness in the hands. In August 2011, the patient underwent an autologous intrathecal stem cell transplant at a different institution, without any changes in her progressive deterioration rated by ALS Functional Rating Scale-revised (ALSFRS-r).

By December 2011, she had lost all motor function in the left upper limb, and bilateral arm fasciculations were observed. Strength in the lower extremities was 2/4. She had difficulty lifting her head and torso in bed. Her respiratory function at rest remained normal. The institutional review board of the Neurology and Neurosurgery Institute, Tecnológico de Monterrey, approved inclusion of the patient in the autologous stem cell transplant research protocol. After informed consent was obtained, she received a subcutaneous daily dose of 300 μg filgrastim (Neupogen; F. Hoffmann-La Roche, Basel, Switzerland) for 3 days. The day after the final dose, peripheral blood mononuclear cells were obtained by leukapheresis (Fenwal CS 3000 Plus; Baxter International, Deerfield, IL, USA). The cell suspension was conjugated with anti-human $CD133^+$ superparamagnetic micro-beads, and linked cells were isolated in a magnetic field over a MiniMACS separation column (Miltenyi Biotech, Bergisch Gladbach, Germany). The isolated $CD133^+$ stem cells (2.5×10^5) from peripheral blood were suspended in 0.3 mL of the patient's cerebrospinal fluid in sterile tubes (4,5).

On June 12, 2012, bilateral stem cell transplantation was performed in the frontal motor cortex with neuronavigation guidance (Vector Vision 2; BrainLab AG, Munich, Germany). The procedure was performed under local anesthesia. No adverse events were registered. Magnetic resonance imaging confirmed the location of the transplant (Figure 1). During the following 6 months after transplantation, ALSFRS-r score remained stable with no decrements. At the end of January 2013, she suddenly presented with respiratory arrest and a generalized seizure, downgrading the ALFRS-r score to 9 points. Tracheostomy and gastrostomy were conducted. At 1 year after transplantation, she remains at home with ventilatory support.

Discussion

ALS rarely occurs in pregnant women. There have been only 17 women with 18 pregnancies reported in the English literature since 1956 (6–16), including the present patient. In this case, the patient first experienced symptoms during the second trimester of pregnancy, and a definite diagnosis of ALS was made 2 months after delivery. Our patient's course resembled cases of rapid progression (13), with ALSFRS-r scores decreasing 20 points over the course of 8 months after delivery, without any response to pharmaceutical or inthrathecal stem cell approaches.

Several treatments have been tested in pregnant patients with ALS (2). So far, stem cell therapy has not been described in these patients. The inclusion of the patient in the present case in stem cell therapy protocols was decided as a last resort. An inthrathecal stem cell transplant was performed 5 months after delivery; the patient showed no clinical

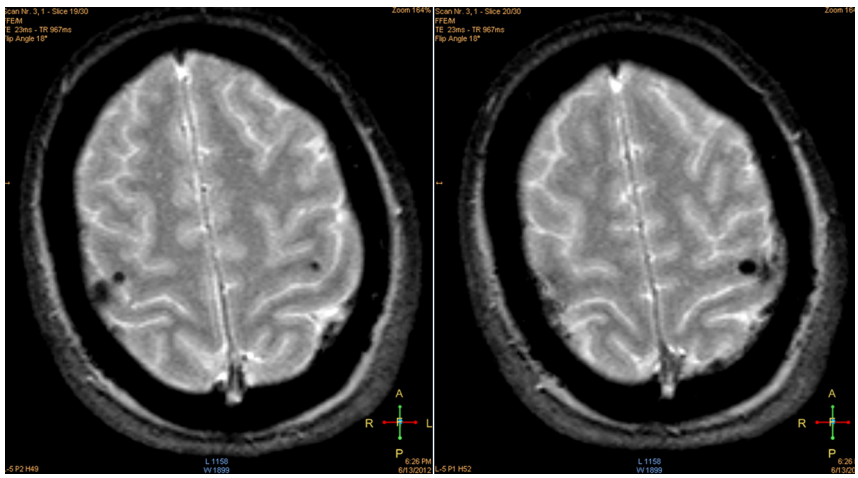

Figure 1. T1-weighted magnetic resonance images in axial view obtained 24 h after stem cell transplantation. Signal void is observed in the frontal motor stripes where stem cells were transplanted.