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Functional MRI in Patients with Cerebral Palsy to Evaluate the Efficacy of Intrathecal Autologous Bone Marrow Total Nucleated Cells

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Abstract

Introduction: In recent years, bone marrow-derived cell therapy has resulted in an alternative treatment for patients with neurological disorders. Research in patients with cerebral palsy undergoing cell therapy has shown improvements in the functionality and quality of life of patients. Functional Magnetic Resonance Imaging (fMRI) is an essential tool that may objectively evaluate the morphological changes in the cerebral tracts after this kind of intervention.

Description of Cases: Three children with a medical history of hypoxic-ischemic encephalopathy were presented. These patients were treated with intrathecal autologous bone marrow total nucleated cells. All three patients demonstrated clinical improvements in their neurological functions. Additionally, fMRI was performed 6, 9, and 10 months, respectively, after the intervention. An increase in anisotropy fraction was observed when evaluated by specialized MRI radiologists, which correlated with their improvements.

Discussion: It has been demonstrated that hematopoietic progenitor cells promote neurogenesis and angiogenesis in brain tissue affected by hypoxic-ischemic injury. This report seeks to add the idea of using fMRI to evaluate improvements after interventions where stem cells are used. However, it is necessary to extend the number of patients to determine if it is the best objective evaluation method for these patients.

Keywords: Functional MRI; Cerebral palsy; Stem cell therapy; Clinical improvement

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Introduction

Cerebral Palsy (CP) is a non-progressive condition secondary to an insult to the central nervous system during its development. It is characterized by abnormal muscle tone that leads to posture and movement. The incidence is estimated at 2-3 per 1,000 births [1].

At present, the use of hematopoietic stem cells has generated interest in medical practice due to their regenerative, reparative, and plastic properties [2], mainly when used in patients with permanent organ damage, such as in CP [3].

Evidence supports that brain functional Magnetic Resonance Imaging (fMRI) is valuable and may evaluate the improvement of patients with CP after different treatments with SC, specifically the white matter, which can be demonstrated with the anisotropy fraction of fMRI [4].

Objective

To describe fMRI as an objective evaluation tool for patients with CP after administering Intrathecal (IT) autologous Bone Marrow Nucleated Cells (BM-TNC).

Case Description

We present three pediatric patients with neurological deficits due to hypoxic-ischemic encephalopathy. They received intrathecal autologous BM-TNCs after three days of Bone Marrow (BM) stimulation with Granulocyte Colony-Stimulating Factor (G-CSF). Basal fMRI was obtained and compared with a second fMRI performed 6, 9, and 10 months, respectively, after treatment.

Table 1: Evaluation of corticospinal tracts by diffusion tensor magnetic resonance imaging with measurement of the Fraction of Anisotropy (FA) at different levels.

	FA Right		FA Left	
	Control	Baseline	Baseline	Control
Patient 1				
Corona radiata	0.34	0.361	0.301	0.41
Posterior limb of the internal capsule	0.433	0.482	0.431	0.431
Cerebral peduncle	0.344	0.372	0.351	0.356
Patient 2				
Corona radiata	0.38	0.38	0.27	0.28
Posterior limb of the internal capsule	0.54	0.55	0.5	0.58
Cerebral peduncle	0.39	0.39	0.51	0.51
Patient 3				
Corona radiata	0.34	0.48	0.31	0.44
Posterior limb of the internal capsule	0.43	0.45	0.37	0.43
Cerebral peduncle	0.43	0.5	0.33	0.52

Case 1

A 34-month-old male, twin pregnancy, extreme prematurity, weighting 1,150 g, Apgar score 6 and 8 at 1 and 5 min, respectively. Neonatal respiratory distress syndrome was treated with NCPAP and caffeine; ductus arteriosus was hemodynamically significant and treated with ibuprofen and pulmonary hyperinflation.

Transfontanelar Ultrasound (TUS) and Magnetic Resonance Imaging (MRI) demonstrate grade 3 intraventricular hemorrhage and multicystic encephalopathy with the right cerebral hemisphere involved. The patient was admitted to the Neonatal Intensive Care Unit (NICU) for 3 months. Afterward, he was diagnosed with spastic quadriparesis CP. He was not able to achieve cephalic and body trunk support, neither to feed on his own, did not communicate or interact with the environment, and was unable to follow objects with his eyes.

An fMRI was performed before the procedure. BM was stimulated with G-CSF at a subcutaneous dose of 10 μg/kg/day for 3 consecutive days. On the 4th day, a BM collection was performed under sedation in both posterosuperior-superior iliac crests. A volume of 8 ml/kg of weight was aspirated. The BM was centrifuged, and the buffy coat was isolated and administered IT [5]. The number of BM-TNC cells infused was 89.76×10^6 CD34+ cells, as measured by flow cytometry.

Ten months after the therapy, he has full head and trunk support, crawling with limb support, executes simple orders, takes objects with both hands, with a predominance of the right hand, babbling, socializing, and interacting with their surroundings.

Baseline and control MRI comparison showed characteristics of periventricular leukomalacia secondary to a hypoxic-ischemic event, with no significant changes between the two studies. The first fMRI showed intact corticospinal tracts, with decreased thickness and size at the corona radiata level, without evident changes when comparing both studies. However, an increased anisotropy was documented in the fMRI, which was more evident in the left corona radiata. These findings correlate with the clinical improvements observed in the patient.

Case 2

A 30-month-old female, 31 weeks of gestational age, 1,800 grams of weight, Apgar score 5/7 at 1/5 min; neonatal respiratory distress syndrome was treated with CPAP.

TUS and MRI: Cortical and coronal decrease of the corpus callosum, intraventricular hemorrhage, and enlargement of the subarachnoid space in the frontal lobes. She stayed in the NICU for two months. She was diagnosed with Hypoxic-Ischemic Encephalopathy (HIE) with spastic quadriparesis CP and developmental delay, clinically without head support, unable to feed herself, and unable to communicate or interact with the environment.

The same procedure was performed as in case 1. The total number of BM total nucleated cells infused intrathecally was 93.0×10^6 CD34+ cells, as measured by flow cytometry.

Nine months after treatment: Complete head and trunk support, improvement in communication with simple sentences of two or three words, interaction with the environment, staying in four points, and remaining seated.

fMRI with Diffusion Tensor Imaging (DTI) performed before and 10 months later demonstrated findings corresponding to hypoxic-ischemic events with no significant changes between both studies. Tractography showed intact corticospinal tracts, with decreased fiber thickness at the corona radiata level without evident differences between studies. In addition, DTI was performed, comparing the anisotropy fraction, demonstrating an increase in the values of the 2nd study, which is more evident at the left posterior limb of the internal capsule level. Like the first patient, these findings correlated with the clinical improvement she presented.

Case 3

A 22-month-old female, born at 41 weeks, 3,850 grams of weight, Apgar score of 2/4 at 1/5 min, 5/7 at 10/15 min. Neonatal respiratory distress syndrome was treated with mechanical ventilation for seven days and then with CPAP, parenteral nutrition by central venous access, and enteral feeding for 23 days.

TUS and MRI: Multicystic encephalomalacia, diagnosed with HIE with CP spastic quadriparesis and developmental delay. Clinically, without head and trunk support, poor management of respiratory secretions, feed by gastrostomy, absence of communication abilities, neither interaction with the environment, and inability to follow objects.

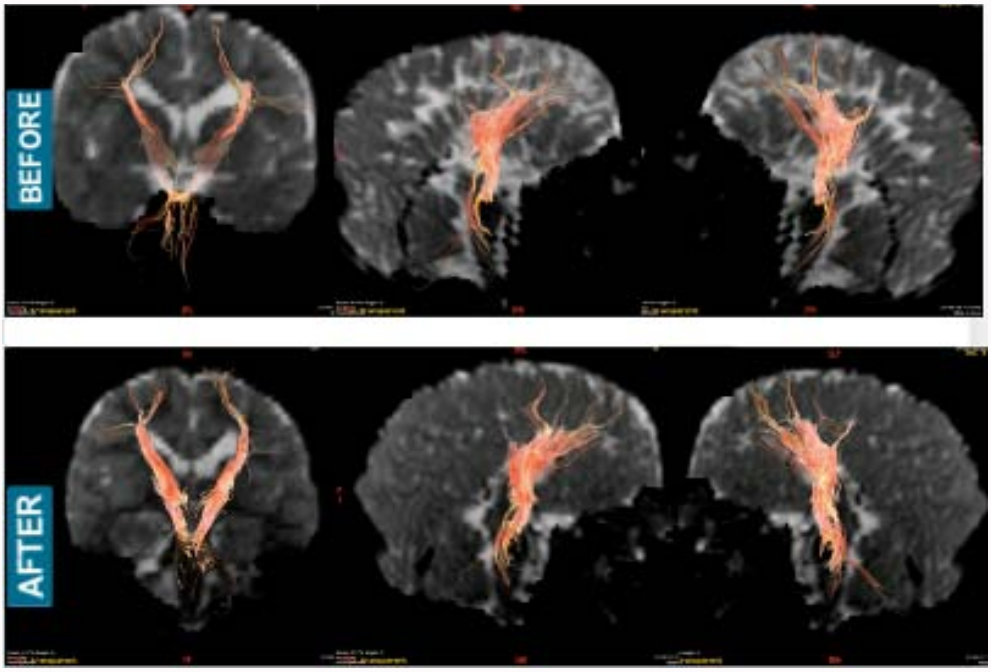

Figure 1: Comparison of the magnetic resonances obtained in clinical case 1.

Autologous BM TNCs were delivered IT the same way as the patients described above. The total amount of BM TNCs infused was 11.76×10^6 of CD34+ cells, as measured by flow cytometry.

Six months later, the patient could reduce the anticonvulsant dose per kilo of weight, interact with the environment, and has a social smile.

Discussion

TNCs have a minimal capacity for transdifferentiation into neurons compared with other progenitor cells. So, how can we explain the improvement of patients with therapy? Evidence suggests that the benefits obtained through treatments such as this one is due to immunomodulatory effects since they migrate to sites where there is inflammation and cell damage and have a chemotactic impact [6], secrete many bioactive molecules that promote cell regeneration [4] and angiogenesis [7].

This has been evidenced by the fact that this type of cell has been used successfully in therapies of another nature, where the damaged tissue is not of the hematopoietic lineage, such as neurons [8], skeletal muscles, and kidneys [9].

Conventional imaging methods have not proved to be useful for objectively measuring improvements in patients with CP. The fMRI is a more sensitive and invaluable tool that can impartially dimension the changes and improvements after stem cell therapy. In addition, this can give us better evidence of neurogenesis and angiogenesis.

Because CP does not have a conventional or specific treatment owing to its complexity and does not boost regardless of standard treatments, as rehabilitation, stem cell therapy could be a therapeutic option to improve the quality of life of these patients and their families.

We decided to use the IT route as the route of administration for several reasons. Although the IV route is better in terms of safety, the number of cells administered IV that can cross the blood-brain barrier still needs to be clarified. In addition, it must be considered a loss of cells distributed in other organs (e.g., liver, lung, etc.) [10]. When cells are administered IT, more of these cells are concentrated in the hypoxic areas [11]. The IT route has proven to be safe and tolerated, with side effects such as fever, headache, nausea, vomiting, and stiffness of the neck, which do not last for more than six days [5,12].

fMRI is a tool that can objectively identify changes and improvements after cell therapy, as in the 3 patients mentioned above (Table 1). Unfortunately, conventional imaging methods have not proven to be very useful since the size of ischemia or edema reduction does not directly correlate with the clinical improvements observed in patients [13]. Currently, more sophisticated methods such as fMRI, which, through anisotropy, is more sensitive and allows analysis of the restructuration of the white matter and its fascicles, provide more evidence of neurogenesis and angiogenesis [14]. Although that brain fMRI did not show evidence of morphological changes, an increase in the anisotropy fraction of the cortical tract was found compared to the study performed before treatment (Figure 1). Furthermore, it was also observed an increase in white matter formation.

Conclusion

CP is a condition that does not improve despite current treatments. The application of BM-TNC can enhance neurogenesis and angiogenesis in affected hypoxic-ischemic brain tissue, which could result in an alternative treatment for patients with this condition. This was demonstrated by fMRI in the cases above and can become a powerful tool to objectively evaluate changes in the central nervous system, specifically in the white matter tracts. However, this must be confirmed in large, comparative, randomized, blinded studies.

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