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Stem Cell Transplantation Efficacy in Cerebral Palsy: A Case Report from a Physical Therapist's Perspective

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Abstract

Children with spastic cerebral palsy usually display an elevation in muscle tone, a decline in gross motor functional abilities, feeding problems and visual problems. Studies on stem cell treatment are in their early stages concerning its efficacy for cerebral palsy. The purpose of the current study was to evaluate the efficacy of stem cell transplantation for gross motor functions, fine motor functions, feeding, vision and spasticity in a child with cerebral palsy (CP). A child with spastic CP on Level V of the Gross Motor Function Classification System (GMFCS) was selected for the transplantation of autologous Bone Marrow-derived Mononuclear Cells (BMMNCs). Muscle tone, gross motor abilities, fine motor abilities, feeding abilities and visual abilities were assessed on 4 occasions including 1) before the transplantation, 2) immediately after the transplantation, 3) six months after the transplantation, and 4) one year after the transplantation. No effect of stem cell transplantation was observed in the child concerning gross motor functions, fine motor functions, feeding, vision and the degree of spasticity. Further studies should be carried out on the subject using a different population rather than the one comprising children on Level V of the GMFCS.

Introduction

Cerebral Palsy (CP) is a neurodevelopmental disorder caused by an injury to the immature cerebrum. It leads to motor impairments which cause a reduction in muscle strength, cardiorespiratory function and motor functional activities [1]. In addition to motor dysfunction, CP may also be associated with the impairment of vision, behavior, cognition, communication, hearing, and epilepsy [2].

Cerebral Visual Impairment (CVI), previously known as cortical visual impairment, is defined as a subnormal visual acuity - despite normal ocular examination - due to damage or injury to

the posterior brain lobe or the posterior visual pathways [3]. The association of CVI with CP has been reported previously [4].

Spasticity is a velocity dependent increase in the stretch reflex. It is a common disorder among children with CP which affects their whole body [5], leading to a reduction in their gross motor functions and activity participation [6].

Children with spastic CP usually have feeding and swallowing disorders that expose them to aspiration and malnutrition risks, especially children with spastic quadriplegia [7].

Stem Cells (SCs) are very small cells. They have no phenotype characteristics of any known adult cells such as epithelial, connective, muscle and neural cells. SCs are able to generate new and differentiated cells of the previously mentioned cell types [8, 9].

The sources of SCs are adult body tissues, embryos, mesenchymal and Induced Pluripotent Stem Cells (IPSCs). Adult SCs or somatic SCs exist in the body since the formation of the embryo; they remain in a non-specific state until the body needs them, such as for repairing bone marrow, liver, or blood. There are two main types of SC transplants based on who /donates them: 1) autologous when the SCs come from the same person who gets the transplant and 2) allogenic when SCs come from a matched donor [10].

Autologous SC transplant uses healthy blood SCs extracted from the same body that receives the transplant [11]. Recent studies have shown some potential of using the autologous SC transplant to overcome the tremendous effect of CP on children via transplanting the Bone Marrow-derived Mononuclear Cells (BMMNCs) and concluded that BMMNCs can develop into neural cell tissues [12, 13].

The purpose of this case study was to detect the efficacy of intrathecal infusion of autologous BMMNCs in a 3 years 6 months old child with CP and its effect on the child's gross motor abilities, fine motor functions, vision, feeding and muscle tone. It was hypothesized that using autologous BMMNCs would have no effect on gross motor functions, fine motor functions, vision, feeding and muscle tone on a child with spastic CP.

2. Methodology

2.1. Patient Information

The subject was a female with spastic CP whose age was 3 years, 6 months and 28

days. Spasticity appeared in her both lower limbs and both upper limbs. She was on Level V of GMFCS. She had epilepsy [on Valproic acid (Depakin), Topiramate (Tobamax) and Lioresal (Baclofen)]. Magnetic Resonance Imaging (MRI) showed a diffused brain subvolumia with right sided wallerian degeneration. She had a history of optical impairments (cataract) and underwent a successful operation. She also had CVI.

2.2. Design

This is a single case study repeated on the following four occasions: 1) before the transplant, 2) immediately after the transplant, 3) after six months of the transplant and, 4) after 1 year of the transplant.

Informed assent was obtained from the child's caregivers according to the principles stated in the Declaration of Helsinki [14].

2.3. Materials of Evaluation

Visual Classification Scale (VCS) was used to determine the CVI level [15]. Peabody Developmental Motor Scale-second edition (PDMS-2) was used to determine the gross motor and fine motor functions [16]. Modified Ashworth Scale (MAS) was used to determine the muscle tone [17] and finally, Behavioral Pediatrics Feeding Assessment Scale (BPFAS) [18] was used to evaluate the feeding behavior. The assessment took place on four occasions. The first time prior to the transplant when the child was 43 months old, the second time immediately after the transplant with the child aged 44 months, the third time assessment was conducted after 6 months when the child was 50 months old and finally, it was conducted after 1 year of the transplant when the child was 55 months old.

2.4. Materials of Management

BMMNCs were transplanted into the child in several steps. The first step was the procurement of *Autologous Bone Marrow Cells*. The child underwent general anesthesia and the bone marrow was extracted from the posterior superior iliac crest. The second step was *SCs' isolation*. This step was performed by an accredited laboratory party in Wadi El Neel Hospital. The final step was *SC's infusion* into the child intrathecally (L4-L5).

3. Results

BMMNCs were extracted from the posterior superior iliac spine and infused

intrathecally (L4-L5) and transplanted into a child with spastic CP.

VCS was used to assess CVI. There was no difference in the CVI level and it remained level 3 on all the four occasions (Table1). Level 3 indicates that the child's eye can fix and gaze shift towards a target [15].

PDMS-2 was used to asses both gross and fine motor functions in terms of gross motor quotient, fine motor quotient and total motor quotient. There was no difference in the gross motor quotient (Table 2), fine motor quotient (Table 3) and the total motor quotient (Table 4) on the four assessment occasions.

Table 1. Level of CVI on VCS

Variable	1 st Assessment (Before Transplantation)	2 nd Assessment (Immediately after Transplantation)	3 rd Assessment (After 6 months of Transplantation)	4 th Assessment (After 1 year of Transplantation)
Functiona l Level	Level 3	Level 3	Level 3	Level 3

Table 2. Gross Motor Quotient using PDMS-2

Variable	1 st Assessment (Before Transplantation)	2 nd Assessment (Immediately after Transplantation)	3 rd Assessment (After 6 months of Transplantation)	4 th Assessment (After 1 year of Transplantation)
Gross Motor Quotient	41	41	41	41

Table 3. Fine Motor Quotient Using PDMS-2

Variable	1 st Assessment (Before Transplantation)	2 nd Assessment (Immediately afte Transplantation)	3 rd Assessment (After 6 months of Transplantation)	4 th Assessment (After 1 year of Transplantation)
Fine Motor Quotient	46	46	46	46

Table 4. Gross Motor Quotient Using PDMS -2

Variable	1 st Assessment (Before Transplantation)	2 nd Assessment (Immediately after Transplantation)	3 rd Assessment (After 6 months of Transplantation)	4 th Assessment (After 1 year of Transplantation)
Total Motor Quotient	38	38	38	38

Table 5. Muscle Tone According to MAS

Variable	1 st Assessment (Before Transplantation)	2 nd Assessment (Immediately after Transplantation)	3 rd Assessment (After 6 months of Transplantation)	4 th Assessment (After 1 year of Transplantation)
Right Upper Limb	1	0	1	1
Left Upper Limb	1+	1	1+	1
Right Lower Limb	1+	1	1+	1+
Left Lower Limb	1+	1	1+	1+

Table 6. Behavioral Pediatrics Feeding Assessment

Variable	1 st Assessment (Before Transplantation)	2 nd Assessment (Immediately after Transplantation)	3 rd Assessment (After 6 months of Transplantation)	4 th Assessment (After 1 year of Transplantation)
Total Frequency Score	68	68	68	68
Total Problem Score	20	20	20	20

Muscle tone was assessed using MAS [19]. The assessment of the muscle tone of the four limbs on the four previously mentioned assessment occasions (Table 5) showed that muscle tone only inhibited immediately after transplantation and it returned back to the initial degree in the third and fourth assessments.

Finally, feeding behavior was assessed using BPFAS [20]. There was no difference found in both the total frequency score and the total problem score on the 4 assessment occasion. The child showed a normal feeding behavior (Table 6).

4. Discussion

The current case study was carried out to detect the efficacy of intrathecal infusion of autologous BMMNCs in a 3 years 6 months old child with spastic CP and to study its effects on her gross motor abilities, fine motor functions, vision, feeding and muscle tone. We accepted the null hypothesis which stated that using autologous BMMNCs has no effect on gross motor functions, fine motor functions, vision, feeding and muscle tone of a child with spastic CP.

VCS was selected to evaluate the visual function level as the patient had CVI. VCS characterizes the performance, specifically during visual examination, and it defines each level by indicating a higher degree of visual performance than the previous level [15]. So, it is considered more peculiar than other scales such as Huo Criteria [21].

PDMS-2 was chosen for assessing the gross and fine motor functions due to its accuracy, high reliability and high validity. It was supported by Walting [22], who evaluated the reliability of PDMS-2 using the Cronbach's coefficient alpha. The values among the test items ranged from 0.84 to 0.98, indicating strong associations. The test-retest reliability within the items applicable to age groups had correlation coefficients ranging from 0.73 to 0.96, thus revealing an acceptable test-retest reliability. The inter-rater reliability for test scores had coefficient values of 0.96 to 0.98. As far as the validity is concerned, concurrent validity was examined and the resulting correlations were strong with the values of 0.84 for the fine motor composite and 0.91 for the gross motor composite.

Although the H-reflex and Hoffman Muscle Response (HM) ratio are the most reliable choices to evaluate the degree of spasticity [23], we chose MAS for an ethical reason. As a clinical note, during previous interventions with the same child,

whenever a muscle electric stimulation was used on the child it was followed by an epileptic seizure; although as far as we know there is no evidence that muscular electric stimulation may induce epileptic seizure in epilepsy patients. However, we didn't want to take any risks by using electrophysiologic evaluation methods such as H-reflex and H/M ratio. Since MAS has a strong positive relationship with H/M ratio [24], so the results wouldn't be affected; in addition to the high reliability and validity of MAS for evaluating spasticity in children with CP [25].

Finally, BPFAS was selected to assess the feeding behavior of the child as it remains an effective measure for assessing the feeding behavior [26].

Research on the effect of stem cell therapy on CP patients started during the last decade. Still, there is a lack of research on different populations of CP patients. Our case study showed that there was no effect of the autologous BMMNC transplant on the CVI, gross motor and fine motor functions, muscle tone and feeding behavior of a child with spastic CP.

The results of the current case study are supported by Carroll and Mays [27]. They stated that although stem cell transplantation may be effective in treating acute brain injuries, still there is no evidence that it may improve a chronic illness such as CP. Even in animal models there was no clear evidence of its advantages.

The results are also supported by a research conducted mainly to investigate the safety of BMMNC transplant in children with CP. Although the trial proved that BMMNC transplantation was a safe procedure, yet the MRI evaluation six months after transplantation showed no difference in brain cells [28]. It indicated no further improvement in CP's associated symptoms.

Our results were also confirmed by Steiner et al. [29], who examined the effect of stem cells in an animal model. They revealed that there was no difference between the MRIs of the brains of the individuals in the study and control groups and that there was only a weak neurogenic effect.

In a systematic review by Novak et al. [30] that was conducted to determine the efficacy and safety of stem cells for improving the motor and cognitive functions of patients with CP. It was concluded that there was only a limited improvement in gross motor functions which supports our case study results.

The results and recommendations of the current study are also supported by Faulkner et al. [31]. They mentioned that the evidence of the benefits of stem cell therapy for patients with CP still needs to be investigated.

On the contrary, the results of our case study contradict the findings of a systematic review [32] which concluded that stem cell therapy improves the associated symptoms in patients with CP and also improves their motor development. However, the said review supported our recommendation for the need of further research on this topic as it mentioned only one randomized control trial and only six other researches of different types.

The results of our study also disagree with a case report by Purandare et al. [33], which reported that the intrathecal infusion of autologous BMMNCs seems to be effective, safe and may have promising functional outcomes in patients with CP. Also, the results disagree with another randomized control study which used autologous marrow mesenchymal SCs as a novel treatment for 30 patients with moderate to severe CP (study group). It showed gross motor improvement in the third and sixth months compared with

another 30 patients with CP (control group) [34].

Finally, our results do not conform to the findings of Liu et al. [35], who mentioned that BMMSC transplantation caused a significant improvement in both gross and fine motor functions in children with CP.

5. Conclusion

There was no effect of autologous BMMNC transplant on the CVI, gross motor and fine motor functions, muscle tone and feeding behavior of a child with spastic CP. Hence, it is recommended to carryout randomized control trials in different populations other than children with Level V GMFCS.

Declarations

• Funding

No funding was received for this study.

• Conflict of interest / Competing interests

The author declares no conflict of interest.

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