JOURNAL OF WORLD SCIENCE
https://jws.rivierapublishing.id/index.php/jws
Volume 4 No. 1 January 2025
P-ISSN: 2828-8726
E-ISSN: 2828-9307

EXPLORING THE ROLE OF STEM CELL THERAPY IN IMPROVING COGNITIVE AND PHYSICAL OUTCOMES FOR DOWN SYNDROME PATIENTS

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ABSTRACT
This review explores the benefits of Mesenchymal Stem Cell (MSC) therapy concerning Down syndrome (DS), cognitive and behavioral disorders, and other related physiological complications. Two pediatric patients with DS participated in this study, receiving MSC therapy over six months through a qualitative case study approach. Patient A was a 5-year-old male experiencing moderate developmental delays and recurrent infections. Patient B was a 6-year-old female facing mild intellectual disabilities and difficulties in social interaction. The initial and follow-up assessments conducted at baseline, three months, and six months after treatment revealed that patients A and B significantly improved in linguistic abilities, attention, social interactions, and motor coordination. Moreover, enhancing inflammatory indices, such as CRP and IL-6, indicated effective regulation of the immune response and reduced inflammation. Both patients adhered to the therapy without any reported side effects. Thus, the findings highlight the potential neuroprotective and immunomodulatory effects of MSC therapy, suggesting it may serve as a viable adjunct treatment for DS. However, due to the limited number of participants and the relatively short observation period, some limitations, such as the small group size and brief study duration, should be acknowledged, necessitating further larger-scale trials to validate these results and establish protocols. This study adds to the existing literature on MSCs in neurodevelopmental disorders and aims to provide a foundation for exploring new treatment options for DS.

Keywords: cognitive; down syndrome; physical outcomes; stem cell therapy

INTRODUCTION

Down Syndrome (DS), also referred to as Trisomy 21, is a chromosomal disorder caused by the presence of an additional copy of chromosome 21. DS occurs in about one in 700 live births, making it the most common chromosomal disorder leading to intellectual disability and developmental delay (Hendrix et al., 2021). The condition is characterized by learning disability, motor coordination difficulties, speech/language development disorders, and other related health complications. Medical issues can be inherited and are as follows: congenital heart disease, immunological disorders, increased vulnerability to infections, and elevated likelihood of developing autoimmune diseases (Snyder et al., 2020). Although there has been progress in therapeutic approaches, the existing treatment plans for DS are mainly palliative and, except for physical, speech, and occupational therapies, do not consider DS's biological and physiological mechanisms (Lee et al., 2020).

Recent advancements in stem cell biology have created the foundation for novel therapeutic strategies that seek to regenerate lost/injured tissue, which could point to

disease pathogenesis. Therefore, MSCs are a promising therapeutic tool, especially in genetic and neurodevelopmental disorders such as DS. MSCs are stem cells that can differentiate into several types of cells, including osteocytes, chondrocytes, and adipocytes. They are usually obtained from stem cell sources such as bone marrow, adipose tissue, or umbilical cord blood (Gou et al., 2024; Jalali et al., 2023; Vaheb et al., 2024). More than their differentiation potentials, MSCs have significant immunosuppressive and anti-inflammatory effects, secrete cytokines and growth factors that support tissue remodeling, and suppress chronic inflammation (Peng et al., 2023; Shi et al., 2018). These features make MSCs a possible innovative therapeutic approach for DS patients, commonly associated with chronic low-grade inflammation and immune abnormalities (Bartesaghi et al., 2022).

Several studies have highlighted the potential of Mesenchymal Stem Cell (MSC) therapy in neurodevelopmental disorders. Paprocka et al. (2021) demonstrated the positive effects of MSCs on motor and cognitive functions in children with cerebral palsy and autism spectrum disorders. Gao et al. (2024) reported the anti-inflammatory and immunomodulatory properties of MSCs, which contribute to tissue repair and functional recovery in aging-related disorders. Similarly, Bartesaghi et al. (2022) emphasized the role of MSCs in mitigating neuroinflammation in genetic disorders. However, the application of MSC therapy specifically for DS remains underexplored, presenting an opportunity to fill this gap in research.

This paper aims to analyze two cases of Down syndrome (DS) treated with mesenchymal stem cells (MSCs), focusing on cognitive, behavioral, and physiological changes. These parameters are especially important because DS is often characterized by deficits in executive functioning, social interaction, as well as fine and gross motor skills (Hendrix et al., 2021). Additionally, the study will assess the impact of MSC therapy on specific inflammatory markers and immune system indicators in DS patients, including C-reactive protein (CRP) and interleukin-6 (IL-6), as these markers have been reported to be elevated in individuals with DS (Snyder et al., 2020). Thus, by tracking both neurological development and physical well-being in these children, this research aims to provide a comprehensive view of the benefits of MSC therapy for issues related to DS.

While previous studies have implied that MSCs may have positive effects on neurological and developmental improvements, such as in cerebral palsy and autism spectrum disorders, their use in DS is still limited (Paprocka et al., 2021). This research work, in its present form, provides some preliminary information for researchers and clinicians by establishing the safety, tolerability, and preliminary efficacy of MSC for DS patients. Using specific cases that are described within the framework of this work, the researcher explores opportunities, limitations, and the most promising avenues for further research. Future research endeavors in regenerative medicine entail investigating such treatment approaches to provide a better quality of life to individuals with DS and their families.

Understanding how MSC therapy can address the persistent low-level inflammation and immune imbalance associated with DS is a significant challenge. This study aims to

explore the cognitive, behavioral, and physiological effects of MSC therapy in patients with DS, shedding light on its potential as a comprehensive treatment approach. This research explores the relationship between neurodevelopmental and inflammatory markers as indicators of MSC therapy's effectiveness in DS. The study aspires to provide a more thorough understanding of the disorder by focusing on this interconnection. Previous studies have yet to comprehensively integrate neurological and systemic health aspects in their MSC therapy evaluation.

The findings from this research are expected to offer clinicians, researchers, and families of DS patients valuable preliminary evidence on the safety and efficacy of MSC therapy. Additionally, the study aims to contribute to developing innovative therapeutic strategies that improve the health-related quality of life for individuals with DS and their caregivers.

METHOD

This research employs a qualitative descriptive approach to explore the potential of Mesenchymal Stem Cells (MSCs) in treating individuals with Down Syndrome (DS). This design captures participants' attitudes and evaluates cognition, behavior, and physiology changes post-MSC treatment. Unlike traditional scientific research, the focus here is on identifying specific outcomes that reveal the impact of MSC treatment in real-life settings. The study, conducted at Celltech Stem Cell Center Laboratory and Banking in Jakarta, Indonesia, is backed by accredited organizations, ensuring that it meets international standards in clinical and laboratory practices (Salwa & Kumar, 2021).

Utilizing a case study method allows for an in-depth analysis of the effects of MSC therapy on two pediatric patients with DS, both of whom have previously undergone conventional treatments with limited success. The study tracks cognitive, behavioral, motor, and physiological changes through caregiver reports, clinical assessments, and lab tests. This integrated approach aligns with recommendations from Puranik et al. (2021) and Alghwiri et al. (2020) for a holistic understanding of post-stem cell therapy effects. The population of the study was patients aged 0-18 years suffering from Down syndrome, having previously undergone several conventional treatments with very little success. Among them are two patients purposively selected, a 5-year-old boy and a 6-year-old girl, both presenting moderate to severe developmental delays. The said selection provides a very consistent and comparable basis for baseline characteristics.

The MSCs were isolated from umbilical cord tissue and administered systemically via intravenous infusion, following established safety and preparation protocols (Alvarez-Viejo & Haider, 2022; Salwa & Kumar, 2021). Patients were monitored at baseline, three months, and six months post-treatment, with various data collection methods employed, including cognitive and behavioral assessments, physiological health monitoring, qualitative interviews with caregivers, and adverse event monitoring.

Data were collected at baseline and followed for 3 months and thereafter for 6 months to track progress. Data analysis techniques included qualitative and quantitative methods. Qualitative interviews with caregivers were analyzed for thematic content, seeking similar changes in behavior and cognition. Quantitative data from clinical evaluation and laboratory tests were analyzed statistically to assess the efficacy of MSC therapy. The power of genuinely mixed methods provides an accurate understanding of the impact of treatment.

Data analysis incorporated qualitative and quantitative methods to assess the effectiveness of MSC therapy (Hendrix et al., 2021; Lian et al., 2024). Ethical considerations were strictly adhered to, ensuring informed consent and patient confidentiality in compliance with the Declaration of Helsinki and HIPAA standards (Puranik et al., 2021).

RESULTS AND DISCUSSION

This paper analyzed the cognitive, behavioral, and physiological changes of two DS patients who underwent six months of MSC treatment. The outcome measurements occurred for each patient at pre-treatment or baseline, three months, and six months post-treatment. The findings regarding cognitive/behavioral alterations, physiological well-being, and informal caregivers' findings/measurements are below.

A. Patient A

1. Cognitive and Behavioral Progress

Baseline

At the initial assessment, Patient A, a 5-year-old male, had moderate developmental disabilities that included impaired expressive language and attentional problems. He also demonstrated poor motor development, as gauged by his balance and coordination deficits.

Three Months Post-Treatment

a. **Cognitive Improvements** Patient A displayed significant changes in areas such as understanding language and using words appropriately. The results also showed a slight improvement in the subject's vocabulary and improved reactivity during simple commands and fundamental interactions.
b. **Behavioral Changes**: Being more in touch with people around them and increased interaction and eye contact frequency for the caregiver. He started to initiate play and engage with the family members more often than before.
c. **Motor Skills**: Coordination concerning the limbs was somewhat enhanced, especially in balance and operations such as using hands to hold objects and stack blocks.

Six Months Post-Treatment

a. **Cognitive Gains**: For example, concerning Patient A, the mother mentioned that at six months, her child made further progress in using language expressions and maintaining attention. He used more functional words in communication and could follow complex

sequences of directions. He was able to pay more attention when focused on activities like puzzles or coloring.

b. **Behavioral Adjustments**: Behavioral observations showed progress in social interaction play, including appropriate eye contact and engagement. His caregiver noted increased instances when Jeffery mimicked sounds, short words, and phrases.
c. **Motor Function**: The motor skills assessments revealed signs of reasonable development in the refinement of gross motor movements, such as stability and control during ambulation and stair climbing.

2. Physiological Health Monitoring

Baseline

Patient A had a history of recurrent infections, and his markers of inflammation, such as the CRP and IL-6, were raised.

a. **Three Months Post-Treatment**: Only CRP and IL-6 levels were reduced, which could mean a reduced inflammation process. The infection rate also decreased, so no more infections were observed throughout the three months.
b. **Six Months Post-Treatment**: Patient A presented with less inflammation and more normalized immune cells at the six-month follow-up than a normal baby. Some of the concerns expressed by caregivers included the following: Previous incidences of respiratory infections were reported to have reduced.

B. Patient B

1. Cognitive and Behavioral Progress

Baseline

Patient B, a 6-year-old female patient, has delays in language and social skills. Her speech use was minimal, and she had difficulty staying on task.

Three Months Post-Treatment

a. **Cognitive Progress**: Patient B also improved her attention and responded to questions and commands more often. They noted that she could follow simple commands and demonstrated a better recall of words previously taught to her.
b. **Behavioral Changes**: Changes such as increased attentiveness in caregivers and friendly interactions with other children were also observed. Parents noted that she was starting to engage in social play with peers, play with siblings, and show interest in group exercise.
c. **Motor Skills**: While her overall motor coordination was poor, her gross motor performance improved. She also demonstrated fine motor control, as she could moderately grip objects and handle utensils.

Six Months Post-Treatment

a. **Cognitive Gains**: By six months of age, Patient B exhibited more advanced language skills that included using simple words while making requests and in social engagements. She got to focus for more extended periods, and she was not easily distracted in play and other learning activities.
b. **Behavioral Adjustments**: She showed definite improvement in awareness of her surroundings, including the emotions of people around her and fundamental social interactions with family members, such as playing peek-a-boo. The caregivers highlighted that they observed less frustration and more patience while the children were learning.
c. **Motor Function**: Insignificant progress was made in gross motor function skills. However, Patient B improved his functional scores on climbing stairs, running, and balance, suggesting improved coordination.

2. Physiological Health Monitoring

Baseline

During the assessment, Patient B had mildly increased overall inflammation markers but had fewer infection episodes than Patient A.

a. **Three Months Post-Treatment**: The levels of inflammatory mediators decreased slightly, indicating that the immune system had responded positively to MSC treatment.
b. **Six Months Post-Treatment**: At six months, Patient B's blood test results indicated appropriate decreases in her CRP and IL-6 levels for her age. Regarding her immunity, she reported occasional respiratory issues; however, none suggested a severe infection during the study period, which lasted approximately six months.

Comparative Analysis of Patients A and B

Cognitive and Behavioral Improvements

However, as seen in both patients, cognitive and behavioral aspects gradually improved six months after MSC therapy. Language development and fine motor skills emerged as more salient for Patient A than Patient B, who thrives on interaction and is more attentive (Alghwiri et al., 2020). These improvements are consistent with MSCs' previously reported anti-inflammatory and neuroprotective properties, which may have helped the patient's cognition and motor abilities.

Physiological Health

Both patients showed decreased inflammatory markers, including CRP and IL-6, improved immune health, fewer infections, and overall better health. Based on these outcomes, MSC therapy might have promoted immune regulation and decreased chronic inflammation, which is prevalent in DS.

Safety and Tolerability

Regarding the side effects, no adverse reactions to the MSC therapy were observed in both patients before, during, and even after its implementation. Its safety in these cases points to the therapy's practicality for DS patients, though research on larger samples must be done to confirm the results.

In this case, MSC therapy suggests possible positive effects on the cognitive, behavioral, and physiological outcomes of patients with Down Syndrome (DS). Both patients showed gradual recovery in language, attention, social interaction, and motor functions and reported changes in inflammation and immunity. These results also emphasize the necessity of further preclinical and clinical studies to investigate the effectiveness and safety of MSC therapy for DS over extended periods and further elucidate ideal treatment regimens that produce the most significant effects.

Discussion

The results of this case study indicate that Mesenchymal Stem Cell (MSC) therapy may improve the cognitive, behavioral, and physiological functioning of persons with Down Syndrome (DS). The results revealed that both patients progressed in language abilities, attention, and social behavior, as well as in motor development, which were shown six months after MSC treatment. These cognitive and behavioral improvements are presumably due to the anti-inflammatory and neuroprotective characteristics of MSCs, which might help foster neural restoration and development. Further, lower CRP and IL-6 levels and enhanced immunity in both patients suggest that MSC therapy may effectively regulate the immune system, an essential factor because DS patients experience chronic low-grade inflammation and increased vulnerability to infections. These enhancements are consistent with the findings of prior studies that demonstrate how MSCs effectively facilitate the formation of neurons and decrease inflammation. However, it is crucial to consider that patient response can vary, especially with the two patients included in the study. For Patient A, language and motor functions seemed to improve more than in Patient B, who achieved substantial progress in social interaction and attentiveness; this means that success depends on factors such as initial state of health, age, or specific cognitive profiles.

Utilizing a case study method allows for an in-depth analysis of the effects of MSC therapy on two pediatric patients with DS, both of whom have previously undergone conventional treatments with limited success. The study tracks cognitive, behavioral, motor, and physiological changes through caregiver reports, clinical assessments, and lab tests. This integrated approach aligns with recommendations from Schira et al. (2012) and Wang et al. (2014) for a holistic understanding of post-stem cell therapy effects. The selected cases involve a 5-year-old boy with moderate to severe developmental delays and a 6-year-old girl with moderate to severe intellectual disability, ensuring consistency in baseline characteristics.

The MSCs were isolated from umbilical cord tissue and administered systemically via intravenous infusion, following established safety and preparation protocols (Kern et al.,

2006; da Silva Meirelles et al., 2009). Patients were monitored at baseline, three months, and six months post-treatment, with various data collection methods employed, including cognitive and behavioral assessments, physiological health monitoring, qualitative interviews with caregivers, and adverse event monitoring. Data analysis incorporated qualitative and quantitative approaches to comprehensively assess MSC therapy's effectiveness (Hendrix et al., 2021; Schira et al., 2012). Ethical considerations were strictly adhered to, ensuring informed consent and patient confidentiality in compliance with the Declaration of Helsinki and HIPAA standards (Puranik et al., 2021).

Despite the positive outcomes, certain drawbacks have to be considered, such as only a small number of patients evaluated and the short duration of the follow-up period. More studies with more patients and longer follow-up times are needed to provide deeper insights into the long-term outcomes of MSC therapies and to set adjuvant guidelines. The data presented here suggest that MSC therapy could be a viable and safe approach to DS treatment. It might address objectives that mainstream therapies and medications do not address, as they primarily target symptom alleviation.

CONCLUSION

This paper aimed to discuss the effectiveness of MSC therapy as an intervention in two individuals with Down Syndrome (DS) based on cognitive, behavioral, and physiological changes. Both patients had positive changes in mental and physical functioning, such as improved language, attention, social interaction, and motor function, as well as decreased inflammation and increased immune regulation. These results indicate that MSC therapy can provide additional advantages beyond traditional DS therapy for cognitive and immune system issues. However, the study had drawbacks, such as a small sample size and a relatively small number of follow-up cases. Further research with more patients and longer follow-ups is needed to confirm these results, define the appropriate dosing regimens, and evaluate the safety profile. However, this study does offer a starting point for thinking about MSC therapy as an adjunct for enhancing QoL in those with DS.

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