World Journal of Methodology

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World J Methodol 2025 March 20; 15(1): 95857

DOI: 10.5662/wjm.v15.i1.95857

ISSN 2222-0682 (online)

ORIGINAL ARTICLE

Clinical Trials Study

Advances in the treatment of autism spectrum disorder: Wharton jelly mesenchymal stem cell transplantation

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Specialty type: Cell and tissue engineering

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Galderisi U

Received: April 20, 2024
Revised: June 23, 2024
Accepted: August 2, 2024
Published online: March 20, 2025
Processing time: 161 Days and 21.1 Hours

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Abstract

BACKGROUND

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder with multifaceted origins. In recent studies, neuroinflammation and immune dysregulation have come to the forefront in its pathogenesis. There are studies suggesting that stem cell therapy may be effective in the treatment of ASD.

AIM

To evolve the landscape of ASD treatment, focusing on the potential benefits and

safety of stem cell transplantation.

METHODS
A detailed case report is presented, displaying the positive outcomes observed in a child who underwent intrathecal and intravenous Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) transplantation combined with neurorehabilitation.

RESULTS
The study demonstrates a significant improvement in the child's functional outcomes (Childhood Autism Rating Scale, Denver 2 Developmental Screening Test), especially in language and gross motor skills. No serious side effects were encountered during the 2-year follow-up.

CONCLUSION
The findings support the safety and effectiveness of WJ-MSC transplantation in managing ASD.

Key Words: Autism spectrum disorder; Neurorehabilitation; Stem cell transplantation; Wharton jelly mesenchymal stem cells; Inflammation

Core Tip: According to data of the World Health Organization, autism spectrum disorder (ASD) is observed in approximately 1 in every 100 children. Recent studies have revealed that immune factors and inflammation are effective in the development of ASD. In this study, we applied six doses of Wharton's jelly-derived mesenchymal stem cell therapy to a 4-year-old patient diagnosed with autism spectrum disorder. After the applications, we observed the patient for 2 years. We did not encounter any serious side effects. According to the Childhood Autism Rating Scale values and Denver II Developmental Screening Test values, we detected significant improvements.

Citation: Kabatas S, Civelek E, Savrunlu EC, Karaaslan U, Yıldız Ö, Karaöz E. Advances in the treatment of autism spectrum disorder: Wharton jelly mesenchymal stem cell transplantation. *World J Methodol* 2025; 15(1): 95857
URL: https://www.wjgnet.com/2222-0682/full/v15/i1/95857.htm
DOI: https://dx.doi.org/10.5662/wjm.v15.i1.95857

INTRODUCTION

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition that manifests in various degrees of impairment in social interaction, communication abilities, and repetitive behaviors. Despite its wide-ranging impact, ASD's etiology remains elusive, with research pointing towards a multifaceted interplay between genetic predisposition and environmental factors[1].

Recent investigations have shed light on the intricate pathogenesis of ASD, highlighting the role of neuroinflammation, immune dysregulation, and altered cytokine levels within the central nervous system (CNS)[1,2]. These underlying mechanisms contribute to the neurobiological alterations observed in individuals with ASD, providing insights into potential therapeutic targets.

In the quest for innovative treatment modalities, stem cell therapy (SCT) has emerged as a promising avenue for addressing the core pathophysiology of ASD. Mesenchymal stem cells (MSCs), in particular, have garnered attention for their immunomodulatory and regenerative properties, offering potential benefits in mitigating neuroinflammatory processes associated with ASD[3,4]. Unlike embryonic stem cells, MSCs present minimal ethical concerns and a reduced risk of tumorigenesis, making them an attractive candidate for clinical applications[5].

Among the diverse types of MSCs investigated for ASD therapy, Wharton's jelly-derived MSCs (WJ-MSCs) have gained traction due to their abundance, accessibility, and favorable biological characteristics[6]. Derived from the Wharton's jelly within the umbilical cord, WJ-MSCs exhibit potent immunomodulatory effects and neuroprotective properties, making them a promising candidate for ASD intervention[7].

The application of WJ-MSCs in ASD therapy represents a paradigm shift in treatment strategies, offering a novel approach to addressing the underlying neurobiological abnormalities. By targeting neuroinflammation and promoting neuronal repair and regeneration, WJ-MSCs hold the potential to alleviate ASD symptoms and improve overall functioning in affected individuals.

In this article, we present a comprehensive case report on the utilization of WJ-MSC transplantation in a child diagnosed with ASD. The study aims to elucidate the safety, efficacy, and therapeutic outcomes associated with WJ-MSC therapy, providing valuable insights into its clinical application and potential benefits for individuals with ASD.

MATERIAL and METHODS

Ethics and consent

This article describes a compelling study conducted at the University of Health Sciences, Gaziosmanpaşa Training and Research Hospital (Istanbul, Turkey). The study involved a 4-year-old patient diagnosed with ASD who underwent a comprehensive treatment protocol consisting of intrathecal (i.t.) and intravenous (i.v.) allogeneic WJ-MSC transplantation. The family provided written consent after receiving detailed explanations of potential complications. The procedure was approved by the Turkish Ministry of Health (12.25.2019 / 56733164-203-E.6874).

Characteristics of the WJ-MSC product used

The WJ-MSCs utilized in this study were produced at Liv Hospital Ulus Stem Cell and Regenerative Medicine Center (Beşiktaş, Türkiye), a facility licensed under Good Manufacturing Practices (GMP) and approved by the Turkish Ministry of Health. The umbilical cord tissues employed were sourced from maternal donors who provided written informed consent for donation. Donors were confirmed to be free of communicable diseases through comprehensive testing conducted by the certified donor screening laboratory of Liv Hospital, in accordance with relevant regulations (EMEA/CHMP/BWP/398498/2005, 21 CFR 1271.75, 1271.80, and 1271.85).

Procedure for obtaining and processing umbilical cord tissue: Collection of cord tissue: After delivery of the placenta and umbilical cord, a sterile piece of approximately 20 cm of continuous cord tissue was obtained from placentas of infants delivered *via* elective cesarean section.

Transport and storage: The collected cord tissue was placed in a sterile container filled with tissue transport solution supplemented with antibiotics to maintain sterility during transport.

Transfer to GMP laboratory: Cord tissue samples were then transferred to the GMP laboratory under controlled conditions.

Initial processing: Upon arrival in clean rooms, the cord tissue underwent sterility testing before proceeding with production procedures.

Tissue preparation: Within a biological safety cabinet, the cord lining, umbilical arteries, and vein were meticulously removed from the cord tissue.

Enzymatic digestion: Wharton's jelly was dissected into small pieces, minced, and digested using GMP-grade collagenase enzymes to release MSCs.

Cell culture: The resulting cell suspension was cultured and allowed to grow to confluence over 7-14 days to establish the primary culture (P0).

Subsequent passages: Cells from P0 were passaged (P1, P2, and P3) under controlled conditions to expand and obtain the desired quantity of WJ-MSCs for the intended application.

Quality control

Viability and cell count were assessed at each stage of cell culture. Rigorous quality control assessments included sterility testing, flow cytometry for characterization, evaluation of pyrogenicity, determination of cell count and viability, telomerase enzyme activity testing to assess tumorigenicity, gene expression profiling, and confirmation of absence of mycoplasma and adventitial viruses (Figure 1[8] and Figure 2[8]).

Final product preparation: The WJ-MSCs were suspended in an isotonic solution and sterilely filled into vials ready for injection. As we previously published and described the procedure in detail, the production of the WJ-MSC product involved stringent adherence to GMP guidelines and meticulous quality control measures to ensure safety, efficacy, and consistency of the SCT intended for the treatment of ASD in the study setting. These detailed processes underscore the importance of standardized protocols and robust quality assurance in the development of advanced cell-based therapies [8].

Cell transplant procedure and clinical features

A 4-year-old child suffered from inability to make eye contact, speech delay incompatible with age, crying spells, difficulties with social interaction. The patient, who was evaluated by a child psychiatrist 6 months ago with her current complaints, was diagnosed with ASD. The patient received special training and neurorehabilitation treatments for approximately 6 months. Patient had no history of chronic disease in the patient's medical history and no significant family history. The patient's childhood autism rating scale (CARS) score was found to be 37. Denver II Developmental Screening Test results were Personal-Social Area: 3 years 3 months; Fine Motor Area: 3 years 6 months; Language area: 2 years 2 months; and Gross Motor Area: 4 years 2 months. In the patient's laboratory tests, anemia, leukocytosis, thrombocytopenia/thrombocytosis, renal failure, liver failure, and electrolyte imbalance were not observed. Acute phase reactants were negative. Additionally, hepatitis B/C and human immunodeficiency virus markers were negative. There were no mass lesions, plaques, or similar abnormal findings detected in the patient's cranial magnetic resonance imaging examination. Ventricular dimensions were within normal limits, and hydrocephalus was not considered. Considering that the patient's CARS score and Denver II Developmental Screening Test results were incompatible with her age, the patient

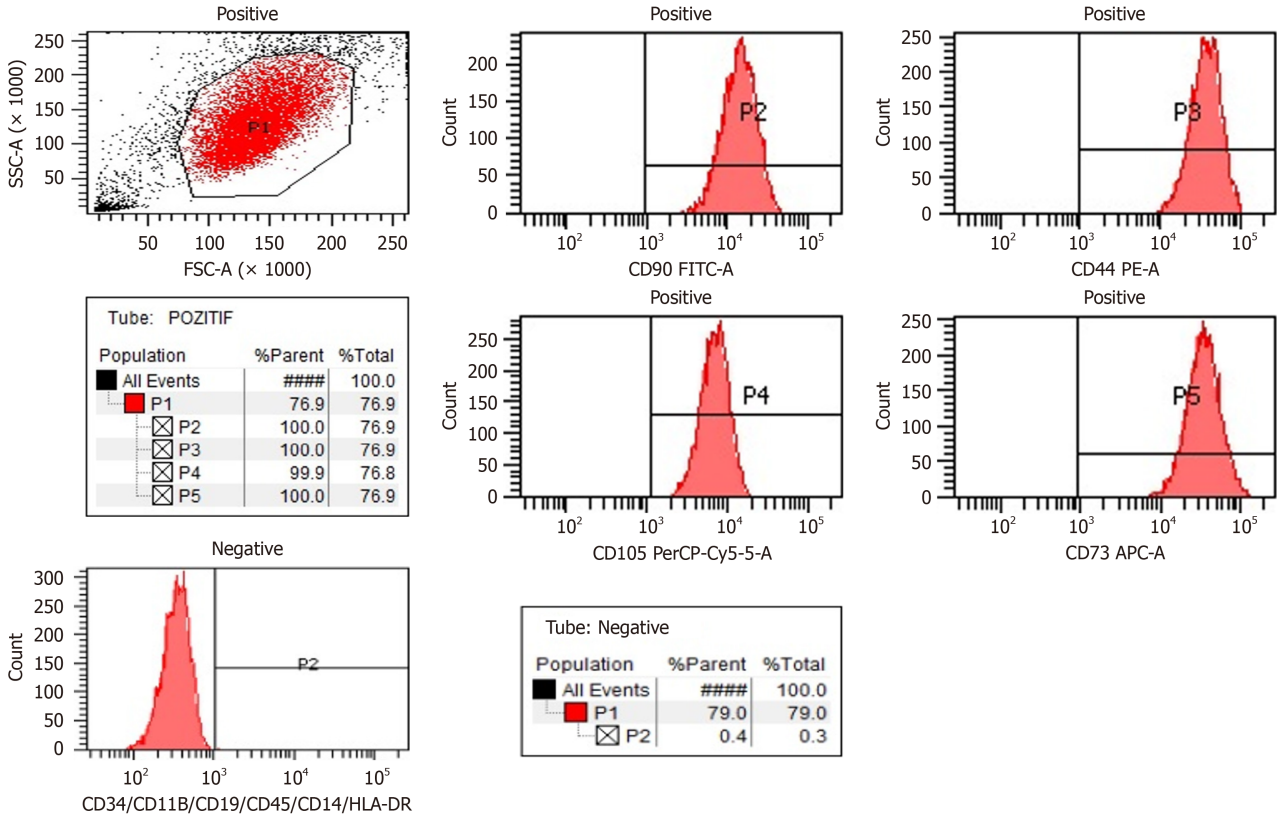

Figure 1 Wharton's jelly-derived mesenchymal stem cell flow cytometry. Positive marker values (cluster of differentiation [CD]90, CD105, CD73 and CD44) are above 95%. Negative marker values (CD45, CD34, CD19, CD11B, human leukocyte antigen-DR and CD14) are below 2%. HLA: Human leukocyte antigen[8]. Citation: Boyalı O, Kabatas S, Civelek E, Ozdemir O, Bahar-Ozdemir Y, Kaplan N, Savrunlu EC, Karaöz E. Allogeneic mesenchymal stem cells may be a viable treatment modality in cerebral palsy. *World J Clin Cases* 2024; 12: 1585-1596. Copyright © The Authors 2024. Published by Baishideng Publishing Group Inc.

was diagnosed with ASD based on the current clinical features.

The treatment protocol included six sessions of i.t. and i.v. WJ-MSCs were administered under sedo-anesthesia. In every instance, the cellular dose was modified to 1 × 10^6 WJ-MSCs/kg of the patient for each of the two application routes. To harness the anti-neuroinflammatory properties and neuro-regenerative capabilities of the MSC product, a dosage of 1 × 10^6 WJ-MSCs/kg was administered i.t. using a spinal needle. Prior to the injection, an equivalent amount of cerebrospinal fluid was extracted to prevent any elevation in intracranial pressure. In addition, a dosage of 1 × 10^6 WJ-MSCs/kg was administered i.v. by a blood infusion set, with the intention of achieving a systemic immune modulation and promoting tissue regeneration.

RESULTS

Remarkably, the treatment demonstrated both safety and efficacy, with no severe adverse events reported throughout the 2-year follow-up period (3rd, 6th, 12th and 24th month). This case study underscores the promising potential of WJ-MSCs transplantation as a therapeutic intervention for ASD and highlights the importance of further research in this area to validate and expand upon these initial findings.

The patient, who initially exhibited a CARS score of 37, experienced a notable improvement, with scores decreasing to 31 after the 6th application. While the Denver II Developmental Screening Test results were compatible with Personal-Social Area: 3 years 3 months, Fine Motor Area: 3 years 6 months, Language area: 2 years 2 months, Gross Motor Area: 4 years 2 months before the applications; after the 6th application, it was evaluated as compatible with Personal-Social Area: 4 years 6 months, Fine Motor Area: 4 years 4 months, Language area: 3 years 9 months, and Gross Motor Area: 4 years 10 months (Figure 3). Positive outcomes were particularly prominent in language and gross motor functions (Video 1 - before treatment, Video 2 - after round 6). No major complication occurred, and minor complications improved with symptomatic treatment (Table 1).

DISCUSSION

The intricate interplay between genetic predisposition and environmental factors in ASD is underscored by recent advancements in single-cell brain organoid screening. Li *et al*[9] identified developmental defects associated with 36 high-

Table 1 Early and late complications

Complications		Administration					
		1st	2nd	3rd	4th	5th	6th
Early	Infection	-	-	-	-	-	-
	Fever	-	+	+	-	-	-
	Pain	+	-	-	-	-	-
	Headache	-	-	-	-	+	-
	Increased C-reactive protein levels	-	-	-	-	-	-
	Leukocytosis	-	-	-	-	-	-
	Allergic reaction or shock	-	-	-	-	-	-
	Perioperative complications	-	-	-	-	-	-
Late	Secondary infections	-	-	-	-	-	-
	Urinary tract infections	-	-	-	-	-	-
	Deterioration of neurological status	-	-	-	-	-	-
	Neuropathic pain	-	-	-	-	-	-
	Carcinogenesis	-	-	-	-	-	-

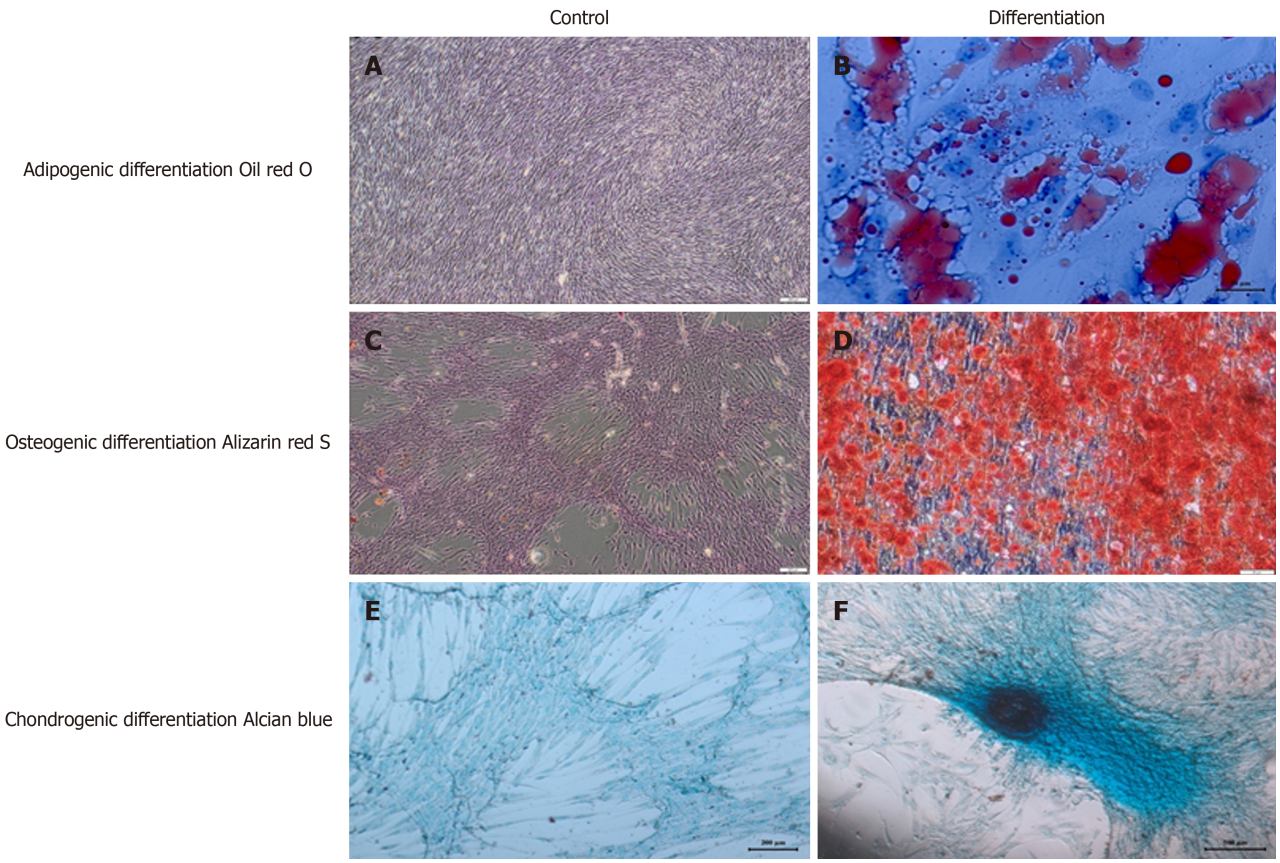

Figure 2 Detection of the differentiation potential of Wharton's jelly-derived mesenchymal stem cells. A and B: Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) were cultured without adipogenic induction and cultured for 3 weeks in adipogenic differentiation medium. Adipogenic differentiation was evidenced by the formation of lipid vacuoles with oil red O staining; C and D: WJ-MSCs were cultured without osteogenic induction and cultured for 3 weeks in osteogenic differentiation medium. Osteogenic differentiation was evidenced by the detection of calcium deposits with Alizarin Red staining; E and F: WJ-MSCs were cultured without chondrogenic induction and cultured for 3 weeks in chondrogenic differentiation medium. Chondrogenic differentiation was evidenced with Alcian Blue staining[8]. Citation: Boyalı O, Kabatas S, Civelek E, Ozdemir O, Bahar-Ozdemir Y, Kaplan N, Savrunlu EC, Karaöz E. Allogeneic mesenchymal stem cells may be a viable treatment modality in cerebral palsy. *World J Clin Cases* 2024; 12: 1585-1596. Copyright © The Authors 2024. Published by Baishideng Publishing Group Inc.

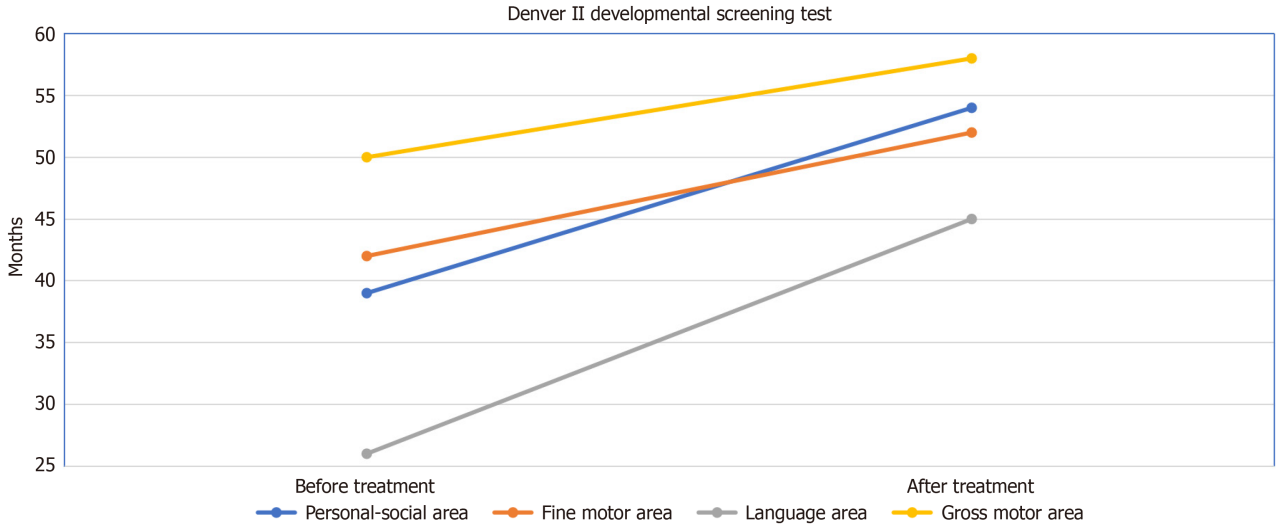

Figure 3 Change of Denver II Developmental Screening test before and after treatment. The rapid improvement in the language area and personal-social area is noteworthy.

risk ASD genes, shedding light on their effects on cell fate determination, particularly in dorsal intermediate progenitors, ventral progenitors, and upper-layer excitatory neurons. This insight emphasizes the relevance of transcriptional regulation in ASD pathogenesis, aligning with our understanding of genetic influences on the disorder.

Exploring neuroinflammation in ASD, recent research by Villarreal-Martínez *et al*[10] aligns with the well-documented inflammatory processes within the CNS. Their findings corroborate dysregulation of proinflammatory processes involving astroglia and microglia, along with abnormal levels of inflammatory cytokines. This concurrence strengthens the evidence for the role of neuroinflammation in ASD and underscores the complexity of its pathophysiology. Nabetani *et al*[11] contribute to the discussion on SCT for ASD, presenting a review that elucidates the new pathophysiological understanding of the disorder. As highlighted, MSCs offer potential as an adjunctive treatment for ASD, aligning with our approach of utilizing allogeneic WJ-MSC transplantation. The review emphasizes the shift towards new paradigms in ASD treatment, reinforcing the relevance and promise of stem cell-based interventions.

One of the most important reasons why we chose WJ-MSCs in our study was that there were many studies in the literature indicating that these cells could be used safely in clinical studies. It is well tolerated by the immune system and thus the risk of rejection is reduced. Additionally, WJCs release dopamine-loaded exosomes that protect against neurotoxicity induced by 6-hydroxydopamine in both two-dimensional (2D) and 3D neuronal cell cultures. Its high immunomodulation feature is especially useful for ASD. In addition to all these, compared to bone marrow MSCs, WJCs exhibit greater expansion capability and faster growth *in vitro*[7].

Our case report aligns with the evolving field of stem cell research and its application in neurodevelopmental disorders. Santos *et al*[12] and Wang *et al*[13] provide additional support by emphasizing the use of induced pluripotent stem cell-derived brain organoids to model ASD. This approach complements our utilization of WJ-MSCs transplantation, indicating the expanding repertoire of stem cell-based models for neurodevelopmental disorders[12,13].

Pertinent to the clinical outcomes observed in our case, Pavinato *et al*[14] describe an autosomal dominant disorder associated with loss-of-function variants in the CAPRIN1 gene. Their findings underscore the importance of understanding specific genetic factors, as in our case, to unravel the genetic basis of neurodevelopmental disorders. Additionally, Liu *et al*[15] identify secretagogin deficiency as a risk factor for ASD, providing further insights into the genetic landscape of ASD and supporting the rationale for individualized treatment approaches.

The advancements in stem cell research and organoid modeling discussed by Li *et al*[9], Santos *et al*[12], and Wang *et al*[13] underscore the need for ongoing research to define optimal stem cell doses and transplantation frequencies. Additionally, the studies by Marinho *et al*[16] and Li *et al*[17] discussing the impact of antidepressants and microRNAs on neurodevelopment highlight the complexity of environmental influences on ASD. These studies contribute to the call for more comprehensive research to refine treatment protocols and enhance our understanding of the intricate mechanisms underlying ASD.

CONCLUSION

In conclusion, the integration of diverse literature strengthens the evidence supporting the safety and effectiveness of WJ-MSCs transplantation in managing ASD. The combination with neurorehabilitation aligns with emerging paradigms in ASD treatment. Promising outcomes in language and gross motor functions suggest the potential of this multifaceted therapeutic strategy to alleviate autism severity. However, the intricate nature of ASD, involving both genetic and environmental factors, necessitates ongoing research for a deeper understanding and refinement of treatment protocols.

FOOTNOTES

Author contributions: Kabataş S and Civelek E contributed to the concept; Kabataş S, Civelek E, and Savrunlu EC, contributed to the design; Kabataş S and Karaöz E contributed to the supervision; Civelek E, Kabataş S, Savrunlu EC, Karaaslan U, and Yıldız Ö contributed to the analysis and/or interpretation; Kabataş S, Civelek E, and Savrunlu EC contributed to the literature search; Kabataş S, Civelek E, Savrunlu EC, Karaaslan U, Yıldız Ö, and Karaöz E contributed to the writing; Kabatas S, Civelek E, and Savrunlu EC contributed to the critical reviews.

Clinical trial registration statement: Our research constitutes a pilot study rather than a randomized controlled trial. Consequently, it was not formally registered. Our intention is for this pilot study to pave the way for future randomized studies.

Informed consent statement: There is human subject in this article and written informed consents were obtained from the patient for their anonymized information to be published in this article and before the stem cell therapies.

Conflict-of-interest statement: All authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

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S-Editor: Liu JH
L-Editor: Filipodia
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