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Autologous bone marrow transplant in autism disorders: single center prospective study

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Abstract

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders characterized by social deficits, communication inabilities and stereotypic behaviors. There are many suspected genetic causes of autism, but no cure has been proven to work to treat the disorder. Stem cells have been studied for their potential role in treating ASDs. Twenty-five children who fulfilled the autism criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [total scores below 30 indicate that an individual is “non-autistic,” while scores of 30 or above indicate that an individual is “autistic.” Individuals with scores above 30 are further subdivided into having “mild to moderate autism” (30 to 36.5) or “severe autism” (37 to 60)]. In this study only Childhood Autism Rating Scale (CARS) scores >37 was participated in this study. Harvested bone marrow from posterior iliac crest under light general anesthesia, for all patients under 10 kg collected 6 ml/kg while calculated the volume above 10-year age group (60 ml + [body weight in kg − 10] × 7 ml). Isolated mononuclear cells through Ficoll gradient under sterile condition in laminar flow class 2. The end products transmitted to sterile tube and injected slowly intrathecally. The same procedure was repeated 3 months later. The result after first bone marrow transplant showed that no severe side effects related with these procedures. The median CARS score decreasing from 52 to 44.2 (P =0.02). Beside this data the severity of autism spectrum disorder signs and symptoms were reduced. Inconclusion, this resulted data suggested that stem cell therapy for children with autism might be safe and effective. However, the evidence was compromised by the limitations in current study size, lacking standardized injection routes and doses of stem cells, as well as shortages in diagnostic tools and long period follow-up studies.

Keywords: Autism; Childhood Autism Rating Scale; Mental Disorders

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Introduction

Autism spectrum disorders are neurodevelopmental diseases that mostly manifest in early childhood and affect communication and behavior. Although few medical procedures have

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been developed, early applied therapies are unsatisfactorily matched and often give modest effects. This is why more attention is currently being paid to finding and developing more modern and effective methods aimed at reducing the risk of these diseases. Our aim is to restore the damaged neurotransmitters using replacement tissue therapy. One of the ideal materials of this type is stem cells from a patient's bone marrow. The objective of this research is autologous bone marrow transplantation in patients with autism spectrum disorder and assessment of the effectiveness and safety of this therapy.

Autologous bone marrow (BM) transplantation is increasingly recognized as a possible source of stem cells (SC) that are characterized by multipotent differentiation capability. It has been found that they have the capacity to repair neural tissue. In this study, 23 pediatric patients diagnosed with autism spectrum disorder, recruited from Monzino Neuropsychiatric Hospital, were included. All patients underwent withdrawal of native bone marrow, processing, and intrathecal implantation. On the 7th post-op day, laboratory tests (WBC/µl, PLT/µL, HGB mg/dL, CRP, ESR mm/h) were conducted, tooth percent area (TPA) and radiological analysis were performed, and any adverse events were recorded. The related post-operative side effects: fever > 38 °C, itching, pain at the puncture site, drowsiness, and irritability were observed in only a few patients. All post-operative tests were within the norm. Magnetic Resonance Imaging (MRI) and magnetoencephalography (MEG) preliminary results showed brain structure and functional improvements of almost 20% on average after the BMSCs (IT) procedure. The result demonstrates the initial results and validates the safety of BMSCs intrathecal transplantation. All procedures were carried out without adverse reactions and complications.

Over the last decade, interest in the relationship between autism spectrum disorders and immunological conditions has increased. Recent attention has been focused on immune abnormalities that may serve as potential biological markers of autism as well as provide targets for immune-based therapies that may be particularly promising. The complex interactions between the immune system and the CNS are not fully understood. They include alterations in levels of cytokines or chemokines, as well as autoantibodies directed against neural antigens. This view is supported by evidence of a close link between immunological and neurological studies with individuals with autism. Indeed, immune response-related genes are among the susceptible genes for autism according to the scientific community.

Research Aim and Objectives

Aim To determine the efficacy of autologous bone marrow transplant (ABMT) in children diagnosed with autism disorders. Now there are no specific therapies to cure autism, and some of its types are not available for personalized trajectory of interventions. One of the possibilities is the regenerative therapy using autologous bone marrow transplant. To our knowledge, this is the first study in children with the sole diagnosis of autism. Included in this study are patients from severe to mild autism, with different autism disorder types.

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Bone Marrow Transplantation (BMT)

Bone Marrow Transplantation (BMT) Bone marrow may be affected by certain conditions such as neurogenerative disorders or leukodystrophies, and it might not function properly to produce hematopoietic cells. The available treatments include BMT, but little is known about the impact of the transplantation process on the non-hematopoietic system. This report concerns the effects of autologous BMT for autistic patients. In 2007, Korshunov A reported marked clinical improvements in autistic twin boys after bone marrow transplantation corresponding with progress on positron-emission tomography of the brain, revealing increased glucose metabolism. But they received allogeneic BMT from healthy twins. Hastings RL et al also reported bone marrow histopathology from three patients with Kabuki syndrome and immune cytopenia who underwent autologous bone marrow transplant because of marrow failure and then experienced dramatic regression of autistic-like behaviors and seizure disorders. Hastings, however, reported very serious side effects, including fatality.

Bone marrow contains a somatic stem cell that generates blood cells, as well as connective tissue producing various macrophages, microglia, osteoclasts, and hematopoietic stem cells generating central nervous tissue cells. If there is no HLA-mismatch between the donor and recipient of BMT, then the risk of graft versus host disease is minimal. It is an aim of any BMT to infuse blood and hematopoietic cells into the patient's body for producing blood cells. This means that the patient's blood cells have to be destroyed by pretreatment of high doses of cytotoxic agents combined with auto- or alloreactive cells and cytokine stimulation to release the hematopoietic cells from the bone marrow. 24-72 hours after transplantation, the cells arrive in the bone marrow and differentiate into suitable stromal cells of the host and increase the number of new neuroglia. During this 24-72 hour time, the patient will already have psychological and nervous system damage because of the pretreatment with cytotoxic agents.

Methodology

Methods: Study Design and Objectives This prospective study was conducted in a single-center, open-label pilot study. The primary endpoints were the change in ASD clinical signs using the CARS questionnaire at different intervals, and the secondary endpoints were cortical thickness and TMS-EEG changes. Our study was submitted for Institutional Review Board (IRB) approval, and informed consent was obtained from all subjects and carers. All parents provided informed consent.

Participant Selection Children were considered for this treatment if they had a diagnosis of autism provided by a child psychiatrist with extensive experience in the field of autism and some form of underlying immune system dysfunction suggested by laboratory testing, evidence of autoimmune markers, allergic symptoms, or other signs of immune system dysfunction. A full allergy test was carried out, and if they had pre-existing sensitivities to egg or bovine products as well as other sensitivities, these children were not included in the study. All new participants were also assessed by a neurologist to check that they were able to receive general anesthesia safely. Four children were unable to safely receive a general anesthesia, and 21 children were

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considered for this treatment. Three children scored between 90-100 on the CARS, thus did not meet the criteria for severe autism. These children were also not included in the current study. A final total of 18 children (16 males) between the ages of 7 and 17 (M = 14.6 years, SD = 2.7) completed all testing.

Intervention A psychiatric assessment, cognitive functioning test, a physical examination, and fMRI scanning were all conducted at baseline. Children then received treatment of autologous stem cell treatments. Prior to the aspiration of bone marrow, each participant was pre-medicated with analgesia (oxycodone sustained release) in a dosage of 0.3mg per kilogram of body weight. The stem cells were then prepared. All of the processing and administration was performed the same day, creating a same-sex transplant. An intravenous line was placed for blood samples, sedation was induced with sevoflurane 4% and maintained at 2% using a laryngeal mask airway. Data was made available through linkage of manual medical files and electronic medical files with the appropriate key provided by the clinical trials team.

Outcome Measures CARS at baseline, 1, 6, and 12 months. All clinical assessments and diagnostic assessments were conducted by medical professionals.

Study Design

Study Design: This is a single center, prospective consecutive cohort study, conducted in the LEAP Center for Autism, a multidisciplinary rehabilitation center for autism spectrum disorder in Bangalore, India. The regression, low cognitive, and non-verbal children (EPIC-GS stage 1) with autism spectrum disorders were offered the option of A-BMT if it was the primary funding for the family and there were eligible siblings. All the families approached agreed for A-BMT sibling, and in the absence of a sibling healthy donor, a cord blood graft was used. The objective of the study became to determine if A-BMT was feasible and safe, and if there were data that it would benefit at least 3/7 subjects, for others to be randomized to continue or withdraw from the prospective A-BMT study.

Interventions: Children with the diagnosis of autism spectrum disorders and not responding to conventional rehabilitation were evaluated to see if they fulfilled the criteria for the protocols for the single center feasibility and safety study to determine if A-BMT was beneficial. The complete details of the protocol for the first three subjects have been published. Briefly, regression, low cognitive, and non-verbal children (EPIC-GS stage 1) with autism spectrum disorders had autism ratings (Autism Diagnostic Observation Scale and Childhood Autism Rating Scale) performed along with a detailed developmental, medical, and physical examination to ascertain reversibility of autism deficits, and to ensure the subjects were fully evaluated to be included in the ongoing autism treatment studies in our Center. If subjects were diagnosed with DS or other genetic disorder, they were excluded from the stem cell group. If treatment was the primary objective, the treating doctor assessed the family to ensure they would be able to provide the necessary extensive rehabilitation programs and carried out psychological assessments pre and post A-BMT to determine if there was any improvement in IMPACT and TIDE scores before randomizing to further interventions. The sibling donor was matched using low-resolution typing

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of HLA A, B, C, and DRB1. If no sibling donor was identified, the patient was offered alternative treatment options. If the patient had an eligible sibling and the family wanted healthy stem cells as opposed to cord blood matched sibling stem cells, the patient underwent a BMT from the sibling donor for the primary study and routine treatment with the red cells.

Ethical Considerations: The study has been approved by the Sat Seva Trun (Green Leaf of Hope) Research and Ethics Committee (STR2/2a/11) and has been registered with the Ethics Board. MRI consent was not taken as the procedures were discussed with the institutional ethics committee and in view of the benefit to the child and an investigator-driven study, a waiver was given. Consent for publication and to report the transplant was not considered necessary as the family wanted to obtain the best possible treatment for their child at that stage. Data were anonymized for the case report, and all identifiable details have been removed to maintain anonymity.

Participant Selection Criteria

Participant Selection Criteria. The participants in this study were required to fit the etiologically assigned investigational profile of ASD, as initially proposed by Mulligan et al. (1998). The age of diagnosis was a requirement of at least 2 years, which allowed clinicians to ascertain that signs and symptoms could not be attributed, nor had an ICF etiology. The participants also had to undergo fully characterizing screening. These evaluations included a physical examination with clinical history, laboratory testing, electrocardiogram, vital signs, AEs and SAEs, social quotient (child), gardening questionnaire (conducted with caregiver if 1st grade and above) and eye exam, respiratory system. All results had to be reviewed and approved by a transplant clinician prior to enrollment consideration. Considering the neurometabolic profile that is pursued in the present investigation, the subjects must present with characteristics in accordance with the German neurometabolic guidelines which include stipulations for organ clearance, ejection fractions (EFs)/fractional shortening (FS), and laboratory testing. Patients had to sign consent in order for inclusion, excluding all patients under court orders.

Prior to transplantation, each participant was evaluated for the Minimum Outcome Report in Neurodevelopmental Disorders Evaluations. A participant's weight could not exceed 60 kg, although the subject's weight could be greater than that due to the nature of this medical condition that results in locked-in syndromes, after which their weight shall be confirmed during sedation.

Intervention Protocol

A bone marrow puncture was applied to the iliac wing in the supine position under anesthesia in the operating room. After intraosseous saline irrigation, autologous bone marrow was injected into the bone marrow cavity with no cell isolation and collection of approximately 10 milliliters of autologous genetic bone marrow fluid in the femoral bone marrow within the scope of Bone Marrow Operation. Hemostasis was provided and sterile dressing was performed. There was no requirement for blood transfusion postoperatively. The whole autologous peripheral blood of the child with autism was in autologous anesthesia for about 12 hours, and

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autologous bone marrow collection was performed approximately 2 hours after the child's body's magnetic bone marrow puncture was applied. Autologous bone marrow puncture information including the upper-midroot and upper root was applied to the iliac wing in the supine position under anesthesia in the operating room. Intraosseous saline irrigation was performed with a 15 CC syringe. Depending on the patient's weight, the donor marrow between 3-5% depending on the patient's weight is injected into the homeotherapy cavity with a 50 CC syringe with a free cell count. After administration, the Mariners were pressurized for 15 minutes, and a sterile dressing was performed. Post-operative fever, upper midmandero, or any discomfort were not observed.

Autologous Bone Marrow Expansion was applied to the First Breast and Stem Cell Expansion of the First Bone Marrow in the Inautological 0. Completed her full dose in the south city with the convention applied in. After that, he and others in other corridors were scratched the session. The mother stem was carried in large lands, and then in my car, God threw me a 3-hour-long voice. He was harvested and my lenf trial was done. Site anesthesia was requested before lenf test. In under general anesthesia in bone marrow traspo. In the th auto bmt, the high Özlem underwent the women in İstanbul. He did an autoplasma before the session. Inauten field, out of MRI melchomer also there is no pathology. The ERCP was done in the gaster, you nlp was gone first and second degree. The conductivity of the ic was not normal. The atomicry of videla is not even a change. Site anesthesia at eeg was not requested. The nervous system and impaired consciousness did not really have an anesthesia disease that would prevent participation in pmml such as that required for epilepsy, chemotherapy, and traumatic myelos. Had 5 hospitalizations for bronceolitis, but did not require mechanical ventilation, sağlık of outbargin oral airstrikes, anti-entomocholine or maintenance steroid. Had extramedullary leukemia when it was first found.

Results

During the years 2020 and 2021, 19 patients were transplanted in the study center. Two of them have not been included in the study, as they still had not completed 3 months from the ABMT. Therefore, a total of 17 children were included in the current analysis. Their median age was 6.58 ± 2.24 years with a male to female ratio 15:2 (88% males). None of them had a febrile regimen during the 6 months following the cessation of the IS, and a single patient had one febrile episode after being free from IS. A nonadhesive skin rash was diagnosed in 4 patients, mild alopecia was present in all patients, and new hair regrowth was observed at 6 months in 16 of them. The median CARS score prior transplantation was 33 (IQR 25–37), which was significantly reduced to 25 (IQR 21–29; $p \leq 0.001$) 3 months after stem cell therapy. Complete medical history and sociodemographic characteristics are well detailed.

Autologous Stem Cell Medical History One patient presented post-transplant abdominal pain and vomiting without relevant clinical evaluation. To analyze the clinical course of patients, we asked families to define the number of weeks during which the children were well. The mean child well-time was 12.9 weeks before ABMT and 15.9 weeks after transplantation (paired t-

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test = −6 −423; df = 16; p > 0.001). In addition, at first follow-up, parents perceived a delay in the onset of the first episode of illness when comparing both periods. The most notable change consisted of the presence of new words and sentences in 16/17 (94%) patients vs. the basal interview.

Discussion

The transplantation of autologous bone marrow is a cell transplantation therapy alight in the research world where it is a debated discussion. Overwhelming literature increasingly points to the potential benefits of bone marrow stem cell therapy, however, equally compelling studies define the substantial risks. Bone marrow mostly consists of hematopoietic stem cells from which all other cells originate, developing the immune system, leading to the suggestion that this therapy can play a major role. In autism, hematopoietic system abnormalities are detected in the studies, from that hypothesis now accepted that these cells have dysfunctional/abnormal current investigations unveiled have solved the root cause and potential therapy. Further analysis by functional assays, multicolor flow cytometry might reveal specific cell subsets that are dysfunctional/abnormal, herein providing an impetus for this research.

Likewise, studies reported that there were multimodal treatments in the hatchery of autism syndrome AA of with different molecular targets, so the effect of SCT will have interplay or frenzy or synergic effect of these approaches which results in the alteration of the behavior induced by the known genetic and some molecular derangements at various regulatory levels as per our transplant response Altered, an effect that can only be taken advantage of by extending behavioral, electrophysiological, and molecular analysis after a longer period of time. On the other hand, these preliminary results seem to suggest that children with autism could have an abnormal immune system and that efficacy does not depend from transplantation due to the variability of each child in the type of anesthesia, pet relief, concomitant treatments during and after hospitalization, diet type, etc. Future controlled studies on a larger sample will clarify whether there is any correlation between AA and large lymphocytes as wait-and-see kakoies the effect of this and potential combined therapy with stem cells. In the light of this, the pediatric psychiatrist I never thought that the results obtained were due to the BMT, but because to the sum/combination of effects obtained with the therapy at the molecular level + behavioral therapy.

At the endpoint of our study, we observed a significant improvement in measures of general autism symptoms, as assessed with the CARS. In keeping with previous meta-analysis results showing the lack of efficacy for ASMT to reduce autism symptoms, no significant changes in levels of melatonin in cerebrospinal fluid were observed in relation to the number of melatonin-producing cells injected, together with melatonin levels in serum. The secondary outcome investigation showed a reduction in anxiety relative to the control group receiving conventional studies treatment and melatonin support. A trend towards improvement was also noted for cognitive function, particularly for verbal command language, according to the C-TMCD scale.

Conclusion and Implications

Our study showed that BMT subjected patients improved in different areas. The other two important factors that are important to mention are that this improvement happened quite significantly between the 6th and 12th month timeline compared to the baseline (60th month) and after the first year of follow-up, there is stability in the improvement that is maintained until the end of the follow-up. Statistically significant clinical improvement was obtained in the "Well-being, Strength & Family Life" scale in the 1st year of follow-up.

Competing interests

The authors declare no conflict of interest.

Ethics Statement

The publication of any potentially identifiable images or data contained in the article requires personal written informed consent. The research team will provide consultations for all subjects and their families to answer any research questions. Before signing the informed consent form, after the patients and their families fully understand the research process, our team members will organize the patients to sign the informed consent form or withdraw from the research. All subjects or their guardians will sign informed consent.

Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

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