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राष्ट्रीय आयुर्विज्ञान आयोग
NATIONAL MEDICAL COMMISSION
आचार और चिकित्सा पंजीकरण बोर्ड
ETHICS AND MEDICAL REGISTRATION BOARD

No. R-13014/28/2022/Ethics **Dated the 6th December, 2022**

RECOMMENDATIONS OF THE COMMITTEE ON STEM CELL USE IN ASD

Ethics & Medical Registration Board (EMRB) of the National Medical Commission had constituted a committee of experts to examine the issues related to prescription, recommendation or administration of stem cell treatment for Autism Spectrum Disorder (ASD). The committee has finalized its report. The report of the Committee along with its recommendations is enclosed.

Vinay 6/12/2022

(Dr. Vijaya Lakshmi Nag)
Member, EMRB

Encl.: As above.

REPORT OF THE COMMITTEE ON STEM CELL USE IN AUTISM SPECTRUM DISORDER

Sections

1. **Current understanding of ASD**
2. **Stem cells in health and SCT research in ASD**
3. **Well-established clinical uses of SCT**
4. **SCT in ASD - a critical appraisal and recommendations**

SECTION 1: CURRENT UNDERSTANDING OF ASD

Definition and Epidemiology: Autism spectrum disorder (ASD) belongs to group of disorders called neurodevelopmental disorders, which are characterized by delay or disturbance in the acquisition of skills in a variety of developmental domains, including motor, social, language and intellectual development. Defining feature of ASD is impairment in development of social interaction and social communication, with repetitive patterns of behaviours, beginning in the early developmental period. The worldwide prevalence of ASD is 0.76% as per the World Health Organization (WHO). Prevalence in India is estimated to be around 1-2/1000. ASD occurs in all racial, ethnic, and socioeconomic groups, and is about 3 times more common in boys.

Clinical features, nature, course and early diagnosis: ASD is a chronic condition with onset in early childhood, with core symptoms that often persist throughout the lifespan. However, its manifestations and severity may vary from person to person, and with age. Impairment in social communication manifests as failure of back and forth communication, Impairment in non-verbal communicative behaviours, and failure to initiate or respond to social interactions. They are often seen to be 'in their own world', having no interest in people or interacting with people and have difficulty in developing and maintaining relationships and friendships. Restricted, repetitive patterns manifest as stereotyped repetitive motor movements, insistence on sameness, or highly restricted, fixated interests. Diagnosis is based on meticulous history, careful clinical evaluation by an expert supplemented by standardised checklists, rating scales and interviews. There is no "specific test" or physical investigation to diagnose ASD.

Early diagnosis is imperative for developing an early intervention strategy in ASD. Checklists such as Modified checklist for autism for toddlers (M-CHAT) are useful in identifying children at risk for ASD.

Comorbidities: A subset of individuals with ASD may have co-existing other developmental medical and behavioural problems. These comorbidities often exacerbate core features and bear a significant impact on activities of daily living. **Developmental comorbidities** include intellectual disability, severe speech and language impairments, and attention deficit hyperactivity disorder (ADHD). **Medical comorbidities** comprise epilepsy, sleeping and feeding disorders, and underlying genetic conditions. **Behavioural / psychiatric comorbidities** include hyperactivity, irritability, agitation, aggression, self-injurious behaviors, anxiety, mood disturbances, and obsessive compulsive disorder.

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Causative factors: Both genetic and environmental factors and a complex interplay between these 2 factors has been implicated in the aetio-pathogenesis of ASD. Some well-known genetic conditions include Fragile X syndrome, Rett syndrome, tuberous sclerosis, certain inherited neurometabolic disorders and copy number variations. However, no single pathogenic variant contributes to more than 1% of all ASD cases. Other proposed mechanisms include aberrant immune activation and a leaky Gut-Brain axis with altered intestinal microbiota. Though several hypotheses about the pathogenesis of ASD have been postulated, none of these are conclusive, necessitating further research in this field.

Current status of biomarkers and neurobiological basis: Considerable amount of research has been carried out to identify a specific biomarker (biological characteristics that are objectively measured as indicators of a pathogenic processes) for ASD, in the hope that it can be used as a "specific test" to identify ASD or underlying anomaly that can explain the clinical features of ASD.. These include head circumference growth trajectory, neuroimaging, electrophysiological testing, immune parameters, and genetic / genomic / metabolomic markers. However, none of these anomalies have been found to be consistently and specifically associated with ASD.

Management: There is no treatment that can "cure" ASD. Parent and caregiver education and counselling is the first step, so that it helps them to understand, accept and cope with their child's problem and also learn how to be part of home-based parent mediated intervention. A number of management approaches have been found to be beneficial in improving the core manifestations of ASD, improving their skills and competencies, and reducing comorbid problems. These include behavioral interventions such as **Applied Behavioural analysis (ABA), Naturalistic developmental behavioral interventions such as** Early Start Denver model, speech /language therapy, occupational therapy, educational approaches, and pharmacological management of comorbid problems such as epilepsy, sleep disorders, and behavioral / psychiatric problems. The need physical investigations varies from case to case and may include genetic, metabolic, electrophysiological and neuro-imaging studies. Genetic counselling needs to be carried out whenever needed.

To conclude, ASD is multifactorial in origin with no established cure. Existing evidence supports the role of behavioural, developmental, and educational interventions as the primary therapeutic modalities for children with ASD. Pharmacotherapy may help treat medical and psychiatric comorbidities to some extent, enabling them to function better and benefit more from different therapies.

Suggested Reading:

1. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed., American Psychiatric Association, 2013.
2. Maenner MJ et al. Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2018. MMWR / December 3, 2021 / Vol. 70 / No. 11
3. Hyman SL, Levy SE, Myers SM, AAP Council on children with disabilities, section on developmental and behavioral pediatrics. Identification, evaluation, and Management of Children With Autism Spectrum Disorder. Pediatrics. 2020; 145(1): e20193447

4. Hayes, J., Ford, T., Rafeeque, H. et al. Clinical practice guidelines for diagnosis of autism spectrum disorder in adults and children in the UK: a narrative review. BMC Psychiatry 18, 222 (2018).
5. Schaefer GB, Mendelsohn NJ; Professional Practice and Guidelines Committee. Clinical genetics evaluation in identifying the etiology of autism spectrum disorders: 2013 guideline revisions. Genet Med. 2013; 15(5): 399–407
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SECTION 2: STEM CELLS IN HEALTH AND SCT RESEARCH IN ASD

Introduction: Stem cells are specialized cells which have the ability to develop into many different cell types and possess an infinite capacity of division as they follow asymmetric cell division. There are mainly two categories of stem cells; embryonic stem cells and adult stem cells (nonembryonic or somatic stem cells).

Embryonic stem cells have the capacity to develop into any type of cell, tissue or organ and are responsible for the development of the human embryo into many tissues and organ systems. Modern stem cell technology has rapidly advanced in the past 2 decades and currently it is possible to "grow" pluripotent stem cells in laboratories: these cells are called induced pluripotent stem cells(iPSC's). Embryonic stem cells of any origin are only used in research, mainly for understanding biology of diseases.

Adult stem cells serve as an internal repair system that generates replacements for cells that are lost through normal wear and tear, injury, or disease. Adult stem cells have been identified in many organs and tissues and are generally associated with specific anatomical locations. These stem cells may remain quiescent (non-dividing) for long periods of time until they are activated by a normal need for more cells to maintain and repair tissues.

There are several types of Adult stem cells, of which 2 types of cells have received maximal attention – haematopoietic stem cells which are present in bone marrow and in peripheral blood, and mesenchymal stem cells (MSC's) that are present in many sources such as bone marrow, umbilical cord blood, adipose tissue, dental pulp, Wharton's jelly. The origin of these cells can be autologous(from one's own body) or allogenic (sourced from another person). Modern stem cell technology now has the capacity to obtain, harvest, and grow these adult stem cells in labs. Their low immunogenicity due to absence of HLA-Class II antigen, makes them an ideal candidate for allogeneic transplantation. Such adult stem cells have been used in the clinical trials, after clearance by Institutional Ethics Committees for meeting ethical standards, due to the establishment of their safety. These stem cells are known to possess paracrine, homing, immunomodulatory and multi-directional differentiation capacity, for which they are receiving attention as a potential therapeutic approach.

Stem cell therapy for human diseases: Stem cells have been extensively researched for treating human disease for many years. The most widespread, well-established, and internationally accepted form of stem cell therapy is Hematopoietic stem-cell transplantation (HSCT), and the commonest indications are blood cancers and haematologic disorders. In

addition, there are more than 900 clinical trials using MSCs in different diseases such as neurological and cardiac disorders, but no clear internationally accepted clinical indication has emerged so far.

Review of research on SCT in ASD:
This has been an active area of research for the past many years ; the available evidence can be divided into following 4 types:

Case reports, case series and open label studies: These are phase 1 / phase 2 exploratory studies primarily to obtain preliminary evidence on the feasibility and safety and to some extent on the efficacy. Efficacy reported in these studies is of low quality because of inherent limitations in methodology such as expectancy effect and rater bias. There have been numerous published reports in this category, and they have generally demonstrated that it is feasible to carry out SCT in ASD. Regarding safety, no major safety issues have been noted. However, fever, headache, vomiting, hyperactivity and seizures have been observed. Reports about efficacy has been mixed, and the need for further research has been expressed. It should also be noted that most of these studies had several methodological limitations and flaws such as absence placebo controls, non-blinded assessments, and small sample sizes.

Controlled trials: Five Randomised Controlled Trials / controlled clinical trials have been conducted so far. The largest and a well-designed double-blind randomised placebo-controlled study of SCT in ASD was by Geraldine Dawson et al in 2020. In this study of 180 children with ASD, SCT was given to 119 children with ASD, with 61 controls. At the end of 6 months, there was no difference between cases and controls on any of the primary outcome measures. Another controlled trial by Chez et al from USA also did not find any difference between SCT and placebo. The other 3 trials - 1 from Iran and 2 from China did find some benefit; however, these studies were found to be inadequate in terms of their methodological rigour and therefore the reliability of their results is questionable.
Thus, it can be safely concluded that as of now there is no clear evidence that SCT is efficacious in ASD.

Meta-analyses: Meta-analyses are a systematic statistical procedure to analyse and combine information from all the available studies in a particular area clinical research. They explore both the quality of research as well as efficacy of a specified treatment approach. Two such meta-analyses have been published on SCT in ASD, one in 2021 by Laura Villarreal□Martinez et al, and the other in 2022 by Jiayang Qu et al. Both have noted some gains, but also observed inadequate scientific quality of most research in this area, thereby putting reservations on the findings. The meta-analysis by Villarreal□Martinez et al has also been criticised for including uncontrolled studies thereby biasing the results. Both have pointed out the need for more systematic studies to address the issues of safety and efficacy.

Guidelines and expert opinions: National and international guidelines, including ICMR guidelines are unform in their conclusion that there is insufficient evidence for SCT in ASD and **do not recommend it as a treatment for ASD**, and call for more high-quality research. Many experts in the field have noted prevailing unethical practice of offering SCT as a treatment for ASD. Further, they have expressed concern and warned about indiscriminate promotion and

predatory marketing of stem cell therapies in ASD leading to creation of false hopes, unrealistic expectations, and exploitation of the affected population and their families. Jessica Sun and Joanne Kurtzberg, eminent researchers in this area, have expressed concerns about predatory marketing practices, and unwarranted raising of hopes despite the absence of good quality scientific evidence and exploitation of patients and their families Similarly, Antonio Narzisi in 2022 stated that "The take home message that needs to be considered is that, to date, the scientific evidence on the use of stem cells for the treatment of ASD is insufficient,..." and that offering SCT for ASD in the current state of scientific research is clearly unethical.

In conclusion, there is as yet insufficient and inadequate scientific evidence on efficacy of the SCT in ASD. Therefore, SCT cannot be recommended as it treatment for ASD.

Further reading

https://stemcells.nih.gov/info/basics/stc-basics

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Narzisi A. Haste Makes Waste: There Is No Solid Evidence to Translate the Use of Stem Cells into Clinical Practice for Children with Autism Spectrum Disorder. Brain Sciences. 2022 Jul 27;12(8):992

Dawson G, Sun JM, Baker J, Carpenter K, Compton S, Deaver M, Franz L, Heilbron N, Herold B, Horrigan J, Howard J. A phase II randomized clinical trial of the safety and efficacy of intravenous umbilical cord blood infusion for treatment of children with autism spectrum disorder. The Journal of Pediatrics. 2020 Jul 1;222:164-73

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SECTION 3: WELL-ESTABLISHED CLINICAL INDICATIONS FOR SCT

Background: Hematopoietic stem cells (HSCs) are multipotent primitive cells that can develop into all types of blood cells, including myeloid-lineage and lymphoid-lineage cells (1). HSCs can be found in several organs, such as peripheral blood (PB), bone marrow (BM), and umbilical cord blood (UCB). The most widespread, well-established, and internationally accepted form of stem cell therapy is Hematopoietic stem-cell transplantation (HSCL), and blood cancers and haematologic disorders are the most common indications. This is a procedure that involves infusion of hematopoietic stem-cells into the diseased person. E. Donnell Thomas performed the first hematopoietic stem-cell transplant (hsct) in 1957 as a novel approach of cancer therapy. Since then, the procedure has dramatically evolved. Today, worldwide, more than 50,000 HSCT procedures are carried out yearly for both benign and malignant diseases. In a hsct procedure after a brief course of chemotherapy, radiation, or both, the recipient's damaged native bone marrow cells and immune system are replaced with infused healthy stem cells and immune cells (the graft). Any remaining cancer cells are eliminated by exploitation of the graft-versus-tumour effect. A donor and suitable fit patient are required for successful hsct procedure. The main objective of the majority of transplants is to cure an underlying cancer or hematologic disease

Sources: Peripheral blood, bone marrow, and umbilical cord units are all sources of stem cells. Hematopoietic stem cell transplantation can be autologous (meaning the recipient's own stem cells are harvested) or allogeneic (meaning that the cells come from another donor or one or more umbilical cord blood units). For both autologous and allogeneic transplants, peripheral blood is now the most popular source of stem cells. Stem cells are mobilized from the peripheral blood after granulocyte colony-stimulating factor alone or combination of chemotherapy and growth factors. A graft utilizing stem cells from peripheral blood offers the benefits of a faster recovery of white blood cells and the immune system and lower incidence of graft failure. The incidence of graft-versus-host disease is higher with peripheral blood grafts.

Procedure: In autologous transplantation, stem cells are cryopreserved for later infusion in to same individual after high dose chemotherapy. This type of hsct should be viewed as a form of rescue therapy to lessen toxicity and permits the recipient to recover from the bone marrow aplasia that often accompanies high-dose therapy. The antitumour effect is solely derived from high dose chemotherapy as opposed to the HSCT itself. In allogeneic HSCT, stem cells are collected from another person or less commonly from umbilical cord blood units. The allogenic transplantation functions in two ways. The immune cells in the graft could also recognise malignant cells as foreign and develop a graft-versus-tumour response.

Indications: Lymphoma and multiple myeloma are most common indications for autologous hsct. Acute myeloid leukaemia, acute lymphoblastic leukaemia, myelodysplastic syndromes, and myeloproliferative neoplasms are leading indications for allogenic transplantation. Non-malignant indications for transplantation include severe aplastic anemia, inherited bone marrow failure syndromes, sickle cell disease, transfusion-dependent thalassemia, inherited

immune deficiency syndromes and certain inherited metabolic disorders such as lysosomal storage disorders.

SECTION 4: STEM CELL THERAPY (SCT) IN AUTISM SPECTRUM DISORDER (ASD) – A CRITICAL APPRAISAL AND RECOMENDATIONS

1. Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder. The complexity of ASD comes from range of severity, presence of variety of comorbidities, and aetiological heterogeneity. ASD causes life-long disability; however, they improve with developmental, behavioral, educational, and other interventions, especially when started early in life because of developmental plasticity.

2. Aetiology, pathogenesis and pathophysiology of ASD are poorly understood in spite of decades of research, though there have been some advances in the understanding of the condition. A consistent and reliable neurobiological signature or biomarker of ASD has not yet been found. Both genetic and environmental factors and gene-environment interactions / epigenetic factors have been found to play a role in the causation of ASD. Immunological abnormalities have been found in some cases of ASD mainly in terms of aberrant immune activation, but the findings have been inconsistent. No clear aetiology can be identified in most cases of ASD.

3. Stem cells are special human cells that are able to develop into many different cell types and are capable of self-renewal. They play an important role in repair and regeneration of various tissues and organs in the body. They have been harnessed for research and for therapy. Blood cancers and certain other haematologic disorders are the most well-established and internationally accepted clinical indications for Hematopoietic Stem cell transplantation.

4. SCT has been investigated it as a possible treatment option in ASD, *based on the unproven hypothesis* that this treatment helps in offering neural cell protection by enhancing neural tissue repair and preventing ongoing neuronal damage, thereby reducing the severity of autistic symptoms.

5. In terms of research, there have been numerous case reports, case series, and uncontrolled open label studies. But very few well-designed double-blind randomised controlled studies (RCT's) have been conducted. In general, the quality of research in this area has been poor.

6. The largest and a well-designed double-blind randomised placebo-controlled study of SCT in ASD was by Geraldine Dawson and her co-workers in 2020. In this study of 180 children with ASD, SCT was given to 119 children with ASD, with 61 controls. At the end of 6 months, there was no difference between cases and controls on any of the primary outcome measures. **In conclusion, this well-conducted study with a large sample found that SCT was not effective in ASD.**

7. Two meta-analyses have been published so far on this topic, in the last 1-2 years. Both have noted that scientific quality of most studies has been inadequate. **Therefore, it is not possible to draw any firm conclusions on the efficacy of SCT in ASD.**

8. None of the current international guidelines recommend SCT as a treatment for ASD. Similarly, many eminent researchers and leaders the lack of sufficient scientific evidence. They also have noted prevailing unethical practice of offering SCT as a treatment for ASD. Further, they have expressed concern and warned about indiscriminate promotion and predatory marketing of stem cell therapies in ASD leading to creation of false hopes, unrealistic expectations, and exploitation of the affected population and their families.

9. Obviously, more well-designed and methodologically sound research needs to explore the safety and utility of SCT in ASD.

- **RECOMMENDATIONS:**

  i. **Current Status: Stem cell therapy is <u>not recommended</u> as a treatment for Autism Spectrum Disorder (ASD) in clinical practice.**
  ii. **In view of the above recommendation, use of Stem cell in ASD, its promotion and advertisement will be considered as professional misconduct.**
  iii. **Further research needs to be conducted and encouraged in terms of well-designed Double-blind RCT's to explore the safety and efficacy of Stem Cell Therapy in ASD.**
  iv. **These recommendations will be updated periodically.**

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