American Journal of Medical Case Reports, 2015, Vol. 3, No. 10, 304-309
Available online at http://pubs.sciepub.com/ajmcr/3/10/1

DOI:10.12691/ajmcr-3-10-1

Amelioration of Autism by Autologous Bone Marrow Mononuclear Cells and Neurorehabilitation: A Case Report

Alok Sharma[1], Nandini Gokulchandran[1], Hemangi Sane[2], Avantika Patil[2,*], Akshata Shetty[3], Hema Biju[3], Pooja Kulkarni[2], Prerna Badhe[1]

[1]Department of Medical Services & Clinical Research, NeuroGen Brain and Spine Institute, Navi Mumbai, India
[2]Department of Research & Development, NeuroGen Brain and Spine Institute, Navi Mumbai, India
[3]Department of NeuroRehabilitation, NeuroGen Brain and Spine Institute, Navi Mumbai, India
*Corresponding author: publications@neurogen.in

Received July 30, 2015; Revised August 12, 2015; Accepted August 28, 2015

Abstract Autism is a clinically and etiologically heterogeneous disorder characterized by deficits in social interaction, communication, behavior and cognitive skills. The etiological basis of autism still remains poorly understood despite several attempts to decipher its neuropathology from different perspectives. Presently available treatment modalities address only limited autism-associated symptoms and are at best palliative. In this report, we present the case of a 7 year old boy with autism treated with intrathecal administration of autologous bone marrow derived mononuclear cells (BMMNCs). On regular follow ups conducted at 3 and 6 months post-treatment, clinically significant behavioral, social, communication and cognitive improvements were reported. These findings were well supported by objective improvements on the Indian Scale of Assessment of Autism (ISAA), Childhood Autism Rating Scale (CARS), Clinical Global Impression (CGI) and Pediatric Functional Independence Measure (WeeFIM). The ISAA score improved from 131 to 112, CARS improved significantly from 40.5 (severely autistic) to 32 (mild to moderate autism), along with an improved WeeFIM score from 31 to 36. Severity of illness on CGI (CGI I) changed from 4 (moderately ill) to 3 (mildly ill). Global improvement on CGI (CGI II) was measured at a score of 2 (much improved), along with an efficacy index (CGI III) of 5 showing moderate therapeutic effect. No adverse events were reported throughout the course of the treatment. Through this case report, we demonstrate that treatment with autologous BMMNCs is safe, feasible and has the potential to ameliorate autism.

Keywords: *autism, cell therapy, autologous, bone marrow, mononuclear cells, neurodevelopmental disorder*

Cite This Article: Alok Sharma, Nandini Gokulchandran, Hemangi Sane, Avantika Patil, Akshata Shetty, Hema Biju, Pooja Kulkarni, and Prerna Badhe, "Amelioration of Autism by Autologous Bone Marrow Mononuclear Cells and Neurorehabilitation: A Case Report." *American Journal of Medical Case Reports*, vol. 3, no. 10 (2015): 304-309. doi: 10.12691/ajmcr-3-10-1.

1. Introduction

Autism is a heterogeneous neurodevelopmental disorder characterized by dysfunctions in communication and social interactions, presence of repetitive stereotypical behaviors, restricted interests and cognitive problems. It is the most severe form of autism spectrum disorders (ASDs), which consist of a group of developmental conditions with symptoms observed on a continuum ranging from mild to severe expression [1]. Other conditions along the spectrum include Asperger's syndrome, childhood disintegrative disorder and pervasive neurodevelopmental disorder not otherwise specified (PDD-NOS). The mean age at diagnosis of autism typically ranges from 36 to 120 months, although symptoms suggestive of autism have also been reported at as early as 6 months of age [2,3]. The prevalence of autism has seen a dramatic rise in the last few years; with current rates of 1 in 68 children, according to the United States Centers for Disease Control (CDC) [4]. Most children with autism continue to exhibit autistic traits in adulthood and experience difficulties in developing social relationships, employment, mental health and independent living [5]. The onset of autism has been attributed to various factors like genetic involvement, immune dysregulation, hypoperfusion, environmental factors and anomalies in brain connectivity, yet the core neuropathological basis of this disorder still remains poorly understood. Recent theories also suggest an etiological overlap between ASDs and attention deficit/hyperactivity disorder (ADHD) as deficits in attention and imitation abilities are a core finding in both disorders. Hence, there is significant assumption that ASD and ADHD may constitute two ends of the same spectrum [6]. A diagnosis of autism is usually established by taking into account clinical features and confirmed by assessment on the Diagnostic and Statistical Manual (DSM), a standardized criteria developed by the American

Psychiatric Association [7]. However, there is no investigation available for a definitive diagnosis of autism. Magnetic Resonance Imaging (MRI) of the brain is usually normal. Therefore, functional neuroimaging is now being explored for autism [8].Treatment modalities available for autism involve long term management by speech, behavior and occupational therapies, along with nutritional guidance and pharmacological treatment. Commonly prescribed therapeutics include antipsychotics, serotonin reuptake inhibitors, psychostimulants and mood stabilizers, along with the use of Methylphenidate for treating hyperactivity or attention deficit [9]. Anticonvulsants are also utilized to control seizures in autistic children. However, there is currently no global consensus on a defined "gold standard" treatment approach for autism.

Given the alarming increase in autism prevalence and a lack of definitive treatment methods, there is an increased sense of urgency to identify and develop a novel therapeutic approach. Growing evidence suggests that cell therapy involving transplantation with autologous bone marrow derived mononuclear cells (BMMNCs) has the potential to repair the underlying damaged brain areas in individuals with autism [5,9-15]. These cells have the unique ability of self renewal, immunomodulation and paracrine regulation [5]. Cell therapy has evolved as a safe and feasible treatment option, as these cells are non-teratogenic, abundant, easily obtainable (involving less invasive procedures) and have no ethical issues. In this report, we present a case of autism treated with autologous BMMNCs after showing limited response to conventional therapies. The primary goal of the treatment is to achieve desirable behavioral, social and cognitive improvements in the child.

2. Material and Methods

2.1. Case Presentation

We present the case of a 7 year old boy with autism treated with intrathecal administration of autologous BMMNCs. The boy had a birth history of a post term caesarean section delivery with asphyxia and delayed cry at birth. He had delayed developmental milestones with absence of speech. No family history of autism was reported. He suffered from a febrile convulsion which lasted for 5 minutes at the age of two years. Clinical manifestations included poor eye contact with presence of hyperactivity (sitting tolerance of less than 1 minute) and restlessness. He also had poor imitation skills along with inappropriate emotional responses and play activity. There was a presence of repetitive behavior and behavioral issues like throwing temper tantrums. He also presented with poor social interaction, comprehension and command following, along with attention and concentration deficit. He primarily used non-verbal need based communication. His sleep patterns were reported to be normal. Functionally, he was dependent for all his Activities of Daily Living (ADLs), with no toilet training. Neurologically, he was hypotonic with normal reflexes. He also exhibited sensory issues like phonophobia (fear of loud sounds), affected visual and auditory responses and vestibular hyposensitivity. He was undergoing regular rehabilitation involving occupational and speech therapy which yielded no improvements with respect to social interaction, communication and behavior.

On the Indian Scale for Assessment of Autism (ISAA), his score was 131, while his Childhood Autism Rating Scale (CARS) and pediatric Functional Independence Measure (WeeFIM) scores were 40.5 (severely autistic) and 31, respectively. Severity of illness on Clinical Global Impression (CGI) scale i.e. CGI I was scored at 4. Magnetic Resonance Imaging (MRI) of the brain revealed attenuation of the posterior body of corpus callosum. An electroencephalography (EEG) recorded in sleep state showed interictal, focal with secondary generalized epileptiform activity on bilateral, assymetrical, mild slow background rhythm.

2.2. Procedure

The boy underwent intrathecal administration of autologous BMMNCs. Our protocol is based on the inclusion criterion as per the World Medical Associations Helsinki declaration. It has been reviewed and approved by the Institutional Committee for Stem Cell Research and Therapy (IC-SCRT). The parents of the patient were fully informed about the procedure and a duly filled informed consent form was obtained. Pre-intervention routine blood tests, urinalysis and chest x-rays were carried out to rule out active infection and assess fitness for anesthesia. 300 mcg of Granulocyte colony-stimulating factor (G-CSF) injections were administrated 48 hours and 24 hours prior to BMMNC transplantation, in order to stimulate CD34+ cells and increase their survival and proliferation. A 100 ml volume of Bone marrow was aspirated from the iliac bone. The density gradient separation method was used to obtain Mononuclear Cells (MNCs). The MNCs were then evaluated for $CD34^{+}$ subpopulations by FACS analysis and viable count was calculated and found to be about 96%. Approximately 96×10^{6} MNCs were administered intrathecally immediately post separation, in L4-L5 using a lumbar puncture needle. 1 gm Solumderol in 500 ml Ringer's Lactate (RL) was simultaneously injected intravenously to reduce local inflammation. Due to a history of seizures and abnormal EEG, prophylactic anti-epileptic medication (Levetiracetam 10 mg/kg) was prescribed for 3 months after the procedure. The patient also underwent extensive neurorehabilitation therapy for six months which included occupational, psychological and speech therapies. During neurorehabilitation sessions, effective motor learning and proprioceptive strategies with task oriented training, for real life environment were utilized and successful attainment of functional outcomes were achieved. The boy was evaluated at regular intervals of 3 and 6 months. He was assessed by re-evaluation on the ISAA, CARS, CGI and WeeFIM scales, after six months. No adverse events were reported throughout the course of the therapy.

3. Results

The boy showed significant improvements over a period of six months. Within a week of the therapy, his hyperactivity had reduced by 10%, along with a 20% improvement in eye contact. His sitting tolerance and attention span showed slight improvement. He had also

started playing with toys and his imitation skills improved. The speech therapist reported an initiation of speech (started saying "baba" which means father). On the follow up conducted at three months, there was further reduction in hyperactivity and improvement in eye contact. Command following also improved and there was a considerable reduction in his repetitive behavior. After six months of the therapy, all the above mentioned improvements were well sustained. There was a further 20% reduction in hyperactivity. His social interaction improved as he would try to initiate interaction with other children. He also developed efficiency in carrying out his ADLs. He would attempt to wipe his face, eat by himself and also dress himself. His phonophobia also reduced significantly. Post-treatment, he had an increased awareness of surroundings and was able to recognize his parents and relatives. His ability to learn new tasks, concept forming and problem solving also improved. His mother was able to partially toilet train him by maintaining a regular schedule. He was also attempting to learn new words, along with making up his own words.

On outcome measures, his ISAA score showed a marked reduction from 131 to 112 (Table 1). His CARS score also showed a marked reduction from 40.5 (severe autism) to 32 (mild to moderate autism). On the WeeFIM scale, his score improved from 31 to 36. Severity of illness on CGI (CGI I) was scored at 3 categorizing him as mildly ill, as opposed to a score of 4 (moderately ill) before therapy. Global improvement on the CGI scale i.e. CGI II graded him with a score of 2 (much improved). The efficacy index on CGI (CGI III) revealed moderate therapeutic effect (score 5) which means decided improvement with partial remission of symptoms with no side effects.

Table 1. Pre and Post-treatment ISAA* Score

	Sub-components of ISAA	Score Pre-treatment	Score at 6 month follow up
A.	**Social Relationship & Reciprocity**	**44**	**34**
1	Has poor eye contact	4	3
2	Lacks social smile	5	3
3	Remains aloof	5	4
4	Does not reach out to others	5	4
5	Unable to relate to people	5	4
6	Unable to respond to social/environmental cues	5	5
7	Engages in solitary and repetitive play activities	5	3
8	Unable to take turns in social interaction	5	4
9	Does not maintain peer relationships	5	4
B	**Emotional Responsiveness**	**20**	**17**
1	Shows inappropriate emotional response	4	4
2	Shows exaggerated emotions	5	4
3	Engages in self-stimulating emotions	4	3
4	Lacks fear of danger	3	2
5	Excited or agitated for no apparent reason	4	4
C	**Speech-Language and Communication**	**19**	**17**
1	Acquired speech and lost it	1	1
2	Has difficulty in using non-verbal language or gestures to communicate	4	3
3	Engages in stereotyped and repetitive use of language	1	1
4	Engages in echolalic speech	1	1
5	Produces infantile squeals/unusual noises	4	3
6	Unable to initiate or sustain conversation with others	4	4
7	Uses jargon or meaningless words	2	2
8	Uses pronoun reversals	1	1
9	Unable to grasp pragmatics of communication	1	1
D	**Behavior Patterns**	**19**	**17**
1	Engages in stereotyped and repetitive motor mechanisms	4	3
2	Shows attachment to inanimate objects	1	1
3	Shows hyperactivity/restlessness	5	4
4	Exhibits aggressive behavior	3	3
5	Throws temper tantrums	4	4
6	Engages in self-injurious behavior	1	1
7	Insists on sameness	1	1
E	**Sensory Aspects**	**18**	**18**
1	Unusually sensitive to sensory stimuli	4	4
2	Stares into space for long periods of time	4	4
3	Has difficulty in tracking objects	4	4
4	Has unusual vision	1	1
5	Insensitive to pain	2	2
6	Responds to objects/people unusually by smelling, touching or tasting	3	3
F	**Cognitive Component**	**11**	**9**
1	Inconsistent attention and concentration	4	3
2	Shows delay in responding	5	4
3	Has unusual memory of some kind	1	1
4	Has 'savant' abilities	1	1
	TOTAL	**131**	**112**

The table depicts the child's score on different sub-components of the ISAA measured pre-treatment and at 6 months follow up post-treatment.
*Indian Scale for Assessment of Autism

4. Discussion

Autism is a clinically and etiologically heterogeneous condition. The exact underlying pathophysiology of autism is still unknown, but it is speculated that it results from a complex combination of genetic, immunological and environmental factors [5]. The genetic architecture of autism involves the interplay of rare and common variants and their influence on hundreds of genes [16]. Growing evidence strongly suggests the role of altered brain connectivity (the connectivity theory of autism), neural hypoperfusion and immune dysregulation in the pathogenesis of autism. Recent studies exploring the connectivity theory of autism have identified patterns of both functional hyper- and hypo-connectivity of the brain in autistic individuals as compared to controls [17,18]. Neural hypoperfusion causes a toxic build up of neurotransmitters or metabolites resulting in hypoxia, leading to neural tissue damage [9]. Evidence suggests that the regions of the brain affected by this hypoperfusion correlate well with brain areas responsible for dysregulated functionalities in autism [9,19]. For instance, certain areas of the temporal lobe which are associated with language comprehension, face recognition and social interaction were reported to be hypoperfused in autistic individuals, but not in controls [19]. Hence, it is believed that the severity of symptoms in autism is directly proportional to the degree of hypoperfusion [9]. Numerous studies exploring the role of immune dysfunction in autism have reported anomalies in the peripheral immune system, along with an activation of microglial cells and the innate neuroimmune system [20,21,22]. Analysis of the peripheral blood of autistic children revealed imbalances in the levels of various cytokines like IFN-γ and interleukins (ILs) [20,23]. Imbalance in levels of $CD3^+$, $CD4^+$ and $CD8^+$ subpopulations, along with alteration of B cell and T cell-mediated immunity have also been associated with autism [20,24]. Moreover, an altered function of the blood brain barrier (BBB) caused by neuroinflammation, immune dysregulation and increased inflammatory cytokines has also been observed in autistic children [20,22].

Conventional therapies for autism can be broadly categorized into behavioral and communication, pharmacological and nutritional therapies, along with family based and individual psychotherapy [5]. Presently, only a handful of medications have been licensed for treating a limited number of autism-associated symptoms which include co-morbidities like seizures, anxiety and depression [24]. However, these prescribed medications fail to address the core neuropathology of autism, have marked side effects and are at best palliative [9,12,24]. Various clinical studies exploring different interventions, ranging from anti-inflammatory drugs to hyperbaric oxygen therapy to administration of zinc and oxytocin are being conducted for autism [5].

Cell therapy has emerged as a promising novel treatment modality for otherwise untreatable neurological disorders and the potential applications of autologous BMMNCs for treating autism have been well established [5,9-15]. This therapeutic approach is known to specifically target the underlying pathomechanisms like immune dysfunction and hypoperfusion which are consistently reported in autism [5,9-15]. In this case report, an individual with autism was treated by intrathecal administration of autologous BMMNCs. These cells are a combination of various cell types including hematopoietic cell populations like CD34+ cells and non-hematopoietic cells like mesenchymal stem cells (MSCs), tissue specific progenitor cells and stromal cells [5,9]. The functional effects of BMMNCs arise from an intricate balance between the beneficial effects of these different cell types. After transplantation, these cells exert a positive effect in autism through their unique abilities of immunomodulation, paracrine regulation, multipotency and rapid self-renewal multiplication rates, thereby restoring the underlying altered brain organization [9], [24]. The cells possess the ability of “homing”, wherein they migrate to and target the areas of damage to carry out repair mechanisms [5]. They exert paracrine effects by enabling the production of essential trophic factors like fibroblast growth factor (FGF2), ciliary neurotropic factor (CNTF) and vascular endothelial growth factor [9]. This facilitates angiogenesis, which in turn reduces hypoxia by promoting the clearance of toxic metabolites and perfusion [9]. Immunomodulation is achieved by inhibiting the activity of pro-inflammatory cytokines like TNF-α, IL-1β and INF-γ; along with an increase in anti-inflammatory factors like TGF-β and IL-10 [11,12]. This restores normal brain functions by counterbalancing the dysregulated neuroimmune system and reducing neural damage. Further to these beneficial reparative effects, treatment with autologous BMMNCs is safe and feasible as these cells are abundant, non-teratogenic and easily obtainable (involving less invasive techniques) with no ethical issues [5,9-15].

In this case report, the reparative effects of cell therapy were well supported by clinical improvements as well as on objective scales. The scales utilized were ISAA, CARS, CGI and WeeFIM. The National Trust, Ministry of Health and Family Welfare, and Ministry of Social Justice and Empowerment of the Government of India jointly developed the ISAA for diagnosis and planning intervention for autism [25]. It is a useful and inexpensive tool to monitor the effects of a given therapy. This scale has 40 items categorized under six domains; social relationship and reciprocity, emotional responsiveness, speech language and communication, behavior patterns, sensory aspects and cognitive component [25]. In the present case, the ISAA score reduced from 131 to 112 (Table 1) and correlated well with the observed clinical improvements (improved social interaction and eye contact, initiation of speech, increased awareness of surroundings, reduced repetitive behavior, reduced phonophobia). These improvements were observed in five out of six ISAA domains. The CARS, a scale commonly used for grading autism severity, also showed a significant improvement as the child’s score reduced from 40.5 (severely autistic) to 32 (mild-moderate autism). This shift in severity was also supported by the score on CGI scale. The severity of illness on CGI (CGI I) changed from 4 (moderately ill) to 3 (mildly ill). Global improvement on CGI (CGI II) graded him with a score of 2 (much improved) with an efficacy index (CGI III) of 5 i.e. moderate therapeutic effect. This indicates that there was decided improvement with partial remission of symptoms with no side effects. The CGI is a well established rating

tool which provides a clinician's view of the patient's global functioning prior to and after initiating a study medication [26]. On the WeeFIM scale, the score improved from 31 to 36. This was supported by the boy's ability to become more independent in his ADLs like eating, dressing up and toilet training. These changes noted on well established objective scales demonstrate that cell therapy is an effective therapeutic approach for autism. We postulate that the above improvements were due to enhanced neural network connectivity in the brain. The cell transplantation developed a microenvironment more conducive to neural repair and synaptic connectivity [27]. Along with neurorehabilitation, the neural connectivity was transformed into functional improvements.

Limitations of previously conducted studies exploring the effects of cell therapy in autism are their small sample size, non-randomization and an absence of control groups. Also, these studies do not utilize biomarkers to demonstrate the effects of cell transplantation. Larger scale, multicentre and randomized controlled trials, along with longer period of follow up are required to further establish the efficacy and safety of cell therapy in autism. To substantiate these findings, future studies should also consider the use of neuroimaging techniques like positron emission tomography-computerized tomography (PET-CT) and/or functional magnetic resonance imaging (fMRI) as monitoring tools. Although the present report represents a solitary case, the significant objective improvements further establish the use of autologous BMMNCs and neurorehabilitation as a feasible treatment for autism. The autologous nature of the treatment evades the possibility of graft-vs-host reaction and the intrathecal route of administration is relatively less invasive making this therapy safe and feasible with no ethical issues. Future studies should explore other routes of administration, and transplantation frequency, as well as dosage, types and combination of cells.

5. Conclusion

Cell therapy offers a feasible therapeutic option for otherwise untreatable neurological conditions like autism and represents a great potential for the future of regenerative and molecular medicine. In this case report, the symptomatic improvements observed were reinforced by improvements on well established objective scales. We hypothesize that autologous BMMNCs with standard neurorehabilitation have the ability to ameliorate autism.

References

[1] Lauritsen, M.B., "Autism spectrum disorders", *European Child & Adolescent Psychiatry*, 22 (Suppl 1). S37-S42. Feb.2013.

[2] Daniels, A.M., and Mandell, D.S, "Explaining differences in age at autism spectrum disorder diagnosis: A critical review", *Autism*, 18 (5). 583-597. Jul.2013.

[3] Rogers, T.D., McKimm, E., Dickson, P.E., Goldowitz, D., Blaha, C.D., and Mittleman, G, "Is autism a disease of the cerebellum? An integration of clinical and pre-clinical research", *Frontiers in Systems Neuroscience*, 7 (15). May.2013.

[4] Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators, Centers for Disease Control and Prevention (CDC), "Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2010", *MMWR Surveill Summ*, 63 (2). 1-21. Mar.2014.

[5] Sharma, A., Badhe, P., Gokulchandran, N., Kulkarni, P., Mishra, Priti., Shetty, A., and Sane, H, "An improved case of autism as revealed by PET CT scan in patient transplanted with autologous bone marrow derived mononuclear cells", *J Stem Cell Res Ther*, 3 (139). 2. May.2013.

[6] Biscaldi, M., Rauh, R., Muller, C., Irion, L., Saville, C.W., Schulz, E., and Klein, C., "Identification of neuromotor deficits common to autism spectrum disorder and attention deficit/hyperactivity disorder, and imitation deficits specific to autism spectrum disorder" *European Child & Adolescent Psychiatry*, 1-11. Aug.2015.

[7] American Psychiatric Association, "Autism Spectrum Disorder Fact Sheet", *Diagnostic and Statistical Manual of Mental Disorders*, (5th ed). 2013.

[8] Chen, C.P., Keown, C.L., Jahedi, A., Nair, A., Pflieger, M.E., Bailey, B.A., and Muller, R., "Diagnostic classification of intrinsic functional connectivity highlights somatosensory, default mode, and visual regions in autism", *NeuroImage: Clinical*, 8. 238-245. Apr.2015.

[9] Sharma, A., Gokulchandran, N., Sane, H., Nagrajan, A., Paranjape, A., Kulkarni, P., Shetty, A., Mishra, P., Kali, M., Biju, H., and Badhe, P, "Autologous Bone Marrow Mononuclear Cell Therapy for Autism: An Open Label Proof of Concept Study", *Stem Cells International*, 2013. 13. Jul.2013.

[10] Sharma, A., Gokulchandran, N., Chopra, G., Kulkarni, P., Lohia, M., Badhe, P., and Jacob, V.C, "Administration of autologous bone marrow-derived mononuclear cells in children with incurable neurological disorders and injury is safe and improves their quality of life", *Cell Transplantation*, 21 (Suppl 1). S79-S90. 2012.

[11] Sharma, A., Gokulchandran, N., Sane, H., Bhovad, P., Biju, H., Shetty, A., Kali, M., and Badhe, P, "Cell therapy effects portrayed on positron emission tomography of the brain serve as a new dimension for autism", *Journal of Pediatric Neurology*, 12 (3). 151-156. Aug.2014.

[12] Sharma, A., Gokulchandran, N., Sane, H., Kulkarni, K., Thomas, N., Paranjape, A., and Badhe, P., "Intrathecal Autologous Bone Marrow Mononuclear Cell Transplantation in a Case of Adult Autism", *Autism*, 3 (2). 1-5. Sept.2013.

[13] Sharma, A., Gokulchandran, N., Shetty, A., Sane, H., Kulkarni, P., and Badhe, P., "Autologous bone marrow mononuclear cells may be explored as a novel potential therapeutic option for autism", *J Clin Case Rep*, 3 (7). 2-4. May.2013.

[14] Sharma, A., Chopra, G., Gokulchandran, N., Lohia, M., and Kulkarni, P., "Autologous Bone Derived Mononuclear Transplantation in Rett Syndrome", *Asian Journal of Paediatric Practice*, 15 (1). 22-24. 2011.

[15] Sharma, A., Gokulchandran, N., Shetty, A., Kulkarni, P., Sane, H., and Badhe, P., "Neuropsychiatric Disorder Tackled by Innovative Cell Therapy-A Case Report in Autism", *Journal of Stem Cell Research and Transplantation*, 1 (1). Aug.2014.

[16] De Rubeis, S., He, X., Goldberg, A.P., Poultney, C.S., Samocha, K., et al., "Synaptic, transcriptional and chromatin genes disrupted in autism", *Nature*, 515 (7526). 209-215. Nov.2014.

[17] Nomi, J.S., and Uddin, L.Q., "Developmental changes in large-scale network connectivity in autism", *NeuroImage: Clinical*, 7 (2015). 732-741. Feb.2015.

[18] Kana, R.K., Uddin, L.Q., Kenet, T., Chugani, D., and Muller, R., "Brain connectivity in autism", *Frontiers in Human Neuroscience*, 8 (349). Jun.2014.

[19] Ichim, T.E., Solano, F., Glenn, E., Morales, F., Smith, L., Zabrecky, G., and Riordan, N.H., "Stem cell therapy for autism", *J Transl Med*, 5 (30). 1-9. Jul.2007.

[20] Samsam, M., Ahangari, R., and Naser, S.A., "Pathophysiology of autism spectrum disorders: Revisiting gastrointestinal involvement and immune imbalance", *World Journal of Gastroenterology*, 20 (29). 9942-9951. Aug.2014.

[21] Pardo, C.A., Vargas, D.L., and Zimmerman, A.W., "Immunity, neuroglia and neuroinflammation in autism", *International Review of Psychiatry*, 17 (6). 485-495. Dec.2005.

[22] Noriega, D.B., and Savelkoul, H.J., "Immune dysregulation in autism spectrum disorder", *European Journal of Pediatrics*, 173 (1). 33-43. Jan.2014.

[23] Molloy, C.A., Morrow, A., Meinzen-Derr, J., Scheifer, K., Dienger, K., Altaye, M., and Willis-Karp, M., "Elevated cytokine levels in children with autism spectrum disorder", *Journal of Neuroimmunology*, 172 (1-2). 198-205. Mar.2006.

[24] Siniscalco, D., Bradstreet, J.J., Sych, N., and Antonuci, N., "Mesenchymal stem cells in treating autism: Novel insights", *World Journal of Stem Cells*, 6 (2). 173-178. Apr.2014.

[25] Patra, S., and Arun, P., "Use of Indian Scale for Assessment of Autism in Child Guidance Clinic: An Experience", *Indian Journal of Psychological Medicine*, 33 (2). 217-219. Jul.2011.

[26] Busner, J., and Targum, S.D., "The Clinical Global Impressions Scale: Applying a Research Tool in Clinical Practice", *Psychiatry (Edgmont)*, 4 (7). 28-37. Jul.2007.

[27] Siniscalco, D., Bradstreet, J.J., and Antonucci, N., "Therapeutic Role of Hematopoietic Stem Cells in Autism Spectrum Disorder-Related Inflammation", *Frontiers in Immunology*, 4 (140). Jun.2013.