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Review Article

Improved brain function in an adult case of Intellectual Disability with Autism Spectrum Disorder following Cell Therapy

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Abstract: Intellectual disabilities (ID) are neurodevelopmental disorders characterized by deficits in intellectual functioning and adaptive behavior which includes conceptual, social and practical skills. 1 out of 4 individuals with ID have co-existing autism spectrum disorder (ASD). Recently, cell therapy has shown great potential in management of ID with ASD due to their ability to address the underlying pathophysiology via immunomodulation and synaptogenesis. We administered autologous bone marrow mononuclear cells intrathecally in a 20-year-old male patient diagnosed as ID with ASD. Over 3 years follow up, there were no adverse events and along with symptomatic improvements, IQ scores improved from 46 to 56 and scores on ISAA improved from 134 to 70. Comparative positron emission tomography–computed tomography brain showed improved metabolism in bilateral frontal, temporal cortices and cerebellum. Autologous bone marrow mononuclear cell therapy may be effective to improve quality of life in individuals of ID with ASD even in adulthood.

Keywords: Intellectual disability, autism spectrum disorder, autologous bone marrow mononuclear cells, cell therapy.

Introduction:

Intellectual disabilities (ID) are defined by DSM-5 as neurodevelopmental disorders that begin in childhood and are characterized by deficits in intellectual functioning and adaptive behavior which includes conceptual, social and practical skills [1]. ID has a high prevalence, affecting 1-3% of the population and 1 out of 4 individuals with ID suffer from an additional ASD [2]. ASD comprises a group of neurodevelopmental disorders characterized by two core symptom domains namely social-communication domain and a behavioral domain including fixated interests and repetitive behaviors that may manifest in a myriad of combinations [3]. Current interventions for ID with ASD can be divided into: behavioral and cognitive interventions; nutritional; and pharmacological treatment for co-morbid mental disorders [4,5]. These interventions manage the symptoms to an extent but there are no validated treatments that address the core pathology. Moreover, ID with ASD has known to be an indicator of poorer prognosis for these intensive treatment plans since persons of ID with ASD have needs that are different from people with ID or ASD alone. ID is chronic and affected individuals tend not to grow out of these challenging behaviors lasting the individual's entire lifetime [6-8]. The unmet medical needs and the fact that they tend to be lifelong disorders contribute to the escalating disease burden on affected individuals, their families and society.

Etiological factors contributing to ID include presence of environmental factors such as exposure to toxic substances, nutritional deficiencies, childhood brain infections, prenatal and postnatal complications and genetic factors such as in Down syndrome, Fragile X syndrome [9-11]. However, many cases of ID result from unknown etiology. Studies have suggested aberrant Central Nervous System (CNS) inflammatory mechanisms in different phases of neurodevelopment and adult life that may affect synaptic function and plasticity, to play a role in the pathophysiology of both ID and ASD [12]. Human post-mortem studies have demonstrated aberrant spine morphology and density and dendritic spine impairments indicating a strong co-relation between alteration in structural development of synapses and development of ID and ASD [13-17]. Through the unique characteristics of immune-regulation [18], and synaptogenesis [19], cell therapy using mononuclear cells possesses potential to manage incurable neurological disorders such as ID and ASD. To study the effect of cell therapy in a 20-year old male

patient with ID and ASD, we administered autologous bone marrow mononuclear cells (BMMNCs) intrathecally.

Body Text:

Case presentation

We present a case of a 20-year-old male patient diagnosed as ID with ASD. He presented to us with complaints of difficulty in communication with repetition of words or sentences spoken by others, aggressive behavior, difficulty in identifying shapes and colors and following commands.

There was no significant prenatal history. He was born at full term, assisted with forceps and cried immediately after birth. Postnatally, motor milestones were achieved normally. But, there was a delay in speech and social development. He started speaking in simple, single line sentences at 5 years of age (normal achievement of meaningful speech is by 3 years of age). At age 6, parents noticed repetitive behavior, aggressiveness and self-biting. Schooling had to be stopped due to his aggressive behavior. He was then taken to a psychologist who diagnosed him as a case of ID with ASD with an IQ of 50-55. To control his aggressive behavior, he was given anti-psychotic medications. He was sent to a special school for 3 years; but parents found no change and hence discontinued his schooling. He has been undergoing special education at home since then. At 18 years of age, the patient had two episodes of seizure for which he was given anti-epileptic medications.

On examination, the patient had cognition limitation in the areas of attention, concentration, memory, comprehension, problem solving and abstract thinking. Eye contact, attention and concentration were poor, and he was easily distracted. He had difficulty in following commands. He could follow only simple, one-step commands. The patient displayed an occasional delayed response to being called by his name.

Behavioral issues such as hyperactivity, hitting, biting, tantrums and self-injurious behavior were present. He also exhibited olfactory hyposensitivity with a sniffing behavior.

Communication was affected with presence of echolalia and self-muttering. Inappropriate emotional responses such as laughter was also present.

Functionally, he was partially independent in the activities of daily living (ADLs). Supervision was required for eating, grooming, bathing, dressing and toileting. Verbal instructions were required for grooming.

On the Binet Kamath Test of intelligence, basal age was found to be 84 months and terminal age was found to be 96 months. Overall mental age was found to be 88 months and global IQ calculated was 46, indicating moderate ID.

To understand and assess the co-morbidity, assistive assessment was performed using standardized tools. On Childhood Autism Rating Scale (CARS) his score was 31, suggesting mild to moderate autism. On Indian Scale for Assessment of Autism (ISAA) he scored 134 with disability of 80%. On Functional Independence Measure (FIM) he scored 75. Based on the overall symptoms, on the Clinical Global Impression (CGI) scale, the patient scored 4 in the severity of illness (SI) category, indicating his condition to be moderately ill before intervention.

Electroencephalogram (EEG) displayed abnormal awake EEG record suggestive of generalized seizure discharges. Magnetic resonance imaging (MRI) brain did not display any significant intracranial abnormality. Positron Emission Tomography (PET CT) brain with fluoro-2-deoxyglucose (FDG) was used as a monitoring tool to map the changes in brain metabolism following cell therapy. PET CT scan done before cell therapy showed reduced uptake signifying decrease in metabolism in the bilateral frontal cortex, thalamus, caudate and putamen, medial temporal cortex, cerebellum.

Materials and Method

Patient selection was based on the inclusion criterion as per the World Medical Associations Helsinki declaration [20], reviewed and approved by the Institutional Committee for Stem Cell Research and Therapy (IC-SCRT). The patient's parents were informed about the procedure and a duly filled informed consent was obtained from them for the same. Routine blood tests, chest X-Ray, EEG, MRI and PET CT were performed prior to the procedure. 300 mcg of Granulocyte colony-stimulating factor (GCSF) was administered 72 and 24 hours before the cell transplantation to promote mobilization, survival and multiplication of the cells. On the day of transplantation, 100 ml bone marrow was aspirated from the right anterior superior iliac spine and collected in heparinized tubes and MNCs were separated by density gradient method. Viable count of the isolated MNCs was taken and was found to be 94%. MNCs were checked for CD 34+ count by fluorescence-activated cell sorting (FACS) analysis and were found to be 2.3%. Approximately 1.2×10^8 MNCs were injected intrathecally, in the L4-L5 space. Methyl prednisolone 1 gm in 500 ml Ringer Lactate solution was simultaneously administered intravenously to reduce local inflammation. Because of the history of seizures and an abnormal EEG, prophylactic anti-epileptic medication (levetiracetam 500 mg) was prescribed for 3 months post cell therapy. A multidisciplinary rehabilitation program was followed during the next 4 days of hospital stay with the patient undergoing psychological therapy; special education; occupational therapy; cognitive behavior therapy; play therapy, art sessions and family counseling; physiotherapy; speech therapy and nutritional advice.

A home program was advised, and patient was followed up regularly. No adverse events were reported during the hospital stay or at the subsequent follow ups at 4 months, 1.5 year, 2 years and 3 years, post intervention. A repeat PET CT scan was performed 2 years post cell therapy.

Image Processing

The raw data of both pre-and post FDG-PET scans were quantified and compared to an age matched normal healthy database using CerQuant and NeuroGam software packages (Segami Corporation, Columbia, MD, USA). The post processing procedures include image reorientation, registration and normalization to standard Talairach atlas template.

Results and Discussion:

Results

There were no adverse events reported immediately after the procedure or at subsequent follow ups.

On follow up of 4 months after cell therapy, attention and concentration improved. He could identify colors and shapes. He developed interest in studies with a sitting tolerance of up to half hour for studies. Motor planning improved, and he was now able to fold clothes and operate a computer. Hyperactivity, aggressive behavior and self-biting, irritability and temper tantrums were also reduced.

There was a slight improvement in social interaction. Eye contact had improved. Inappropriate laughter and irrelevant speech also reduced. Echolalia decreased as did stereotypical behavior and olfactory seeking behavior.

On FIM, he improved from 75 to 84.

At 1.5 year follow up; there were improvements in observation, imitation, thinking and reasoning skills. He could now count up to 10 items, write numbers from 1-10, copy alphabets in Marathi. He could form short sentences and showed further improvement in his studies. Parents reported that imitating others had stopped completely. There was an improvement in social interaction and he could hold a conversation. Olfactory seeking behavior had stopped completely. Hyperactivity decreased further and could now sit for an hour. Aggressive behavior and self-injurious behavior had also stopped completely.

On CARS, he improved from 31 to 23.5 (non-autistic).

At follow up of 3 years, the above-mentioned improvement continued and was able to understand non-verbal gestures and could perform some household tasks such as making tea.

On the Binet Kamath Test of intelligence, his mental age was now 108 months (pre-cell therapy: 88 months) and IQ was 56 (pre-cell therapy: 46), corresponding to mild ID (pre-cell therapy: moderate ID). Terminal age was now found to be 120 months (pre-cell therapy: 96 months) (

Table **1**). There was improvement of autistic features. CARS score improved from an earlier 23.5 to 21 (non-autistic). ISAA score improved from 134 (moderate autism) to 70 (mild autism) (Table 2); on FIM his scores improved from 84 to 104. On the Clinical Global Impression (CGI) scale, the severity of index score changed from 4 (moderately ill) to 2 (borderline mentally ill); the global improvement was 1 (very much improved) and the therapeutic efficacy was 1 (moderate improvement, partial remission of symptoms with no side effects)

Table 1: Comparison of Binet Kamath Test of intelligence pre-and post-cell therapy

	Pre-cell therapy	Post-cell therapy
Basal age (in months)	84	84
Terminal age (in months)	96	120
Mental age (in months)	88	108
IQ	46	56
Degree of retardation	Moderate ID	Mild ID

Table 2: ISAA score pre-and post-cell therapy

	Score sub-components of ISAA	**Score pre-treatment**	**Score at 3 years' follow up**
A.	**Social Relationship & Reciprocity**	**42**	**10**
1	Has poor eye contact	5	2
2	Lacks social smile	2	1
3	Remains aloof	5	1
4	Does not reach out to others	5	1
5	Unable to relate to people	5	1
6	Unable to respond to social/environmental cues	5	1
7	Engages in solitary and repetitive play activities	5	1
8	Unable to take turns in social interaction	5	1
9	Does not maintain peer relationships	5	1
B	**Emotional Responsiveness**	**13**	**7**
10	Shows inappropriate emotional response	5	1
11	Shows exaggerated emotions	1	1
12	Engages in self-stimulating emotions	5	2
13	Lacks fear of danger	1	2
14	Excited or agitated for no apparent reason	1	1
C	**Speech-Language and Communication**	**33**	**27**

15	Acquired speech and lost it	1	2
16	Has difficulty in using non-verbal language or gestures to communicate	5	4
17	Engages in stereotyped and repetitive use of language	5	4
18	Engages in echolalic speech	5	4
19	Produces infantile squeals/unusual noises	1	1
20	Unable to initiate or sustain conversation with others	5	4
21	Uses jargon or meaningless words	5	3
22	Uses pronoun reversals	1	1
23	Unable to grasp pragmatics of communication	5	4
D	**Behavior Patterns**	**20**	**11**
24	Engages in stereotyped and repetitive motor mechanisms	5	4
25	Shows attachment to inanimate objects	1	1
26	Shows hyperactivity/restlessness	5	1
27	Exhibits aggressive behavior	3	1
28	Throws temper tantrums	3	1
29	Engages in self-injurious behavior	2	2
30	Insists on sameness	1	1
E	**Sensory Aspects**	**18**	**8**
31	Unusually sensitive to sensory stimuli	1	3
32	Stares into space for long periods of time	5	1
33	Has difficulty in tracking objects	5	1
34	Has unusual vision	1	1
35	Insensitive to pain	1	1
36	Responds to objects/people unusually by smelling, touching or tasting	5	1
F	**Cognitive Component**	**8**	**7**
37	Inconsistent attention and concentration	5	4
38	Shows delay in responding	1	1
39	Has unusual memory of some kind	1	1
40	Has ‘savant’ abilities	1	1

Comparative PET CT brain performed 2 years post cell therapy showed improved FDG uptake in the bilateral frontal cortex involving orbital and medial frontal cortex, caudate head and putamen, temporal cortex including heschl’s gyrus and medial temporal cortex, and in cerebellum as shown in Figure 1and Table 3.

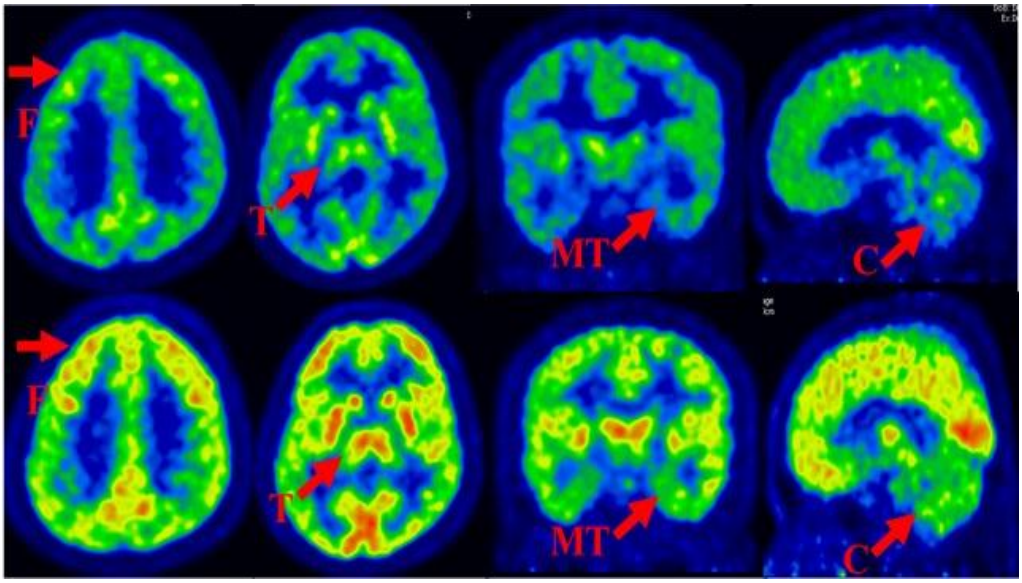

Figure 1: Representative PET CT brain images of the patient with Intellectual Disability and Autism Spectrum Disorder. Top row indicates sections before the intervention of cell therapy. Bottom row indicates PET CT images 2 years post cell therapy. The arrow heads indicate the regions of interest (ROI).

F- Frontal cortex, T-Thalamus, MT-Medial temporal cortex, C- Cerebellum. Post cell therapy showed improved FDG uptake within the ROI.

Table 3: Comparison of quantification of standard uptake values (SUV) on PET CT brain and corresponding functional improvements

Region of Interest	%hypometabolism Pre-cell therapy Right	%hypometabolism Post cell therapy Right	%hypometabolism Pre-cell therapy Left	%hypometabolism Post-cell therapy Left	Improvement in function corresponding to the improvement seen on PET CT post cell therapy
Temporal_Inf	12.78	0.29	5.8	2.53	Visual object recognition, memory and learning, language, emotional control
Temporal_Mid	22.26	14.05	11.41	2.52	
Temporal_Pole_Mi	12.34	0	0	0	
Temporal_Sup	18.58	11.65	16.65	2.08	
Heschl	16.7	17.68	57.74	30.36	
Hippocampus	4.98	0	1.56	0.16	
ParaHippocampal	12.3	0	0.05	0.14	
Fusiform	23.88	0	5.49	4.08	
Cingulum_Post	27.32	26.22	17.81	6.99	Social cognition, Behavior, Executive function and learning
Frontal_Sup_Media	2.8	0	17.11	0.55	
Frontal_Inf_Orb	7.24	0	0	2.55	
Frontal_Med_Orb	24.61	5.22	36.57	15.69	
Frontal_Mid_Orb	25.72	0	0	1.76	
Insula	17.56	15.06	16.33	8.74	
cerebellum	7.89	2.28	7.42	0	Language, social interaction, and improved motor planning and execution (by connections with prefrontal cortex)

Discussion:

Cell therapy has shown to be beneficial in individuals with ID [21-23] and in individuals with ASD [24-32] due to its ability to address the core disease pathophysiology. But its effect on adults of ID with ASD has not been studied. To study its effect in adult patients of ID with ASD we administered autologous BMMNCs in a 20-year-old patient.

Although the exact pathophysiology of ID and co-morbid ASD is not known, but studies have suggested a possible role of

immunological dysfunctions and neuro-inflammation causing synaptic pathophysiology and disruption of the synaptic pathways [12,33]. It has been suggested that alterations of 'in utero' environment, may cause increased levels of circulating cytokines which can either enter the fetal brain parenchyma or lead to a cascade of events in the placenta. Cytokines can affect both synaptic plasticity and behavior [34,35]. Further, studies support the view that this early inflammation affects the brain immune response permanently [36,37]. Tissue homeostasis is maintained by a balance between pro-inflammatory and anti-inflammatory response. Sustained exposure to harmful signals for prolonged time may cause prevailing of microglial activation. There is evidence that microglia can disrupt dendritic branches and spines, the key regulators of neuronal function and essential for formation of neuronal circuits

[38,39] affecting synaptic connectivity. Synaptic connectivity is critical for learning, memory and behavior in the developing and adult brain [40].

Targeting immune dysregulation and restoration of normal synaptic functions is thus an important factor influencing restoration of neurological function and treatment outcome in these patients. Due to their ability to alter immune responses, transplantation of BMMNCs can target the immune dysfunction [18]. The BMMNCs exhibit immuno-modulatory benefits mainly through two mechanisms: cell-to-cell contact activation mechanism, through which the transplanted stem cells produce switching over of pro-inflammatory macrophages to anti-inflammatory macrophages [41]; secretory paracrine activity promoting inhibition of apoptosis, anti-inflammation, immunosuppression, and possible regulation of specific metabolic pathways [42]. BMMNCs possess the ability to migrate to the sites of dysfunction [43] and promote synaptic plasticity thus facilitating functional recovery [44,45].

Significant functional improvements were seen in our patient. The earliest improvements were seen at 4 months post cell therapy which was sustained and continued through the 3 year follow up duration. These improvements were validated objectively on outcome measures used such as Binet Kamath Test of Intelligence, ISAA, CARS and CGI. Binet Kamath Test of Intelligence is an adaptation of Stanford-Binet Scale of Intelligence, amended to suit Indian conditions. It is a standardized scale for the Indian population [46]. Mental age growth reaches an asymptote by age of 14 years [47]. We found an increase in mental age by 20 months post cell therapy in this patient of 20 years of age. ISAA also is a reliable scale designed for the Indian population and enables differentiation between high functioning and low functioning individuals with autism and comorbid psychiatric disorders, including ID [48]. A shift in the severity of the symptoms from moderate to mild in this patient together with improvements in intellectual ability at adult stage signifies that cell therapy played a vital role. Improvement was also seen on CARS, a scale used to grade the severity of autism, with the patient's score decreasing from 31 (mild to moderate autistic) to 21 (non-autistic). CARS serves as a good diagnostic and screening tool to assess adolescents and adults with ASD [49].

The CGI assessment is a widely-used assessment tool measuring illness severity (SI), global improvement (GI) and therapeutic effects (EI). Post cell therapy, our patient moved from 4 (moderately ill) to 2 (borderline mentally ill) in the SI category; scored 1 in the GI category indicating very much improved; and 1 in the EI category indicating moderate improvement with partial remission of symptoms.

PET CT brain was also used as a monitoring tool to map the changes in brain glucose metabolism occurring post cell therapy.

PET CT scan done before cell therapy showed reduced uptake, signifying a decrease in metabolism [50], in the bilateral frontal cortex, medial temporal cortex, basal ganglia, and cerebellum.

The temporal lobe comprises of the primary auditory, the secondary auditory and visual cortex, and the limbic system, and has widespread connections to the rest of the cortex. Afferent projections from the primary and secondary auditory and visual areas end at the temporal pole, posterior parietal cortex, superior temporal sulcus, medial temporal or limbic areas and finally at the hippocampus. Projections from auditory and visual association areas also reach the two prefrontal regions; the dorsolateral and the orbital region [51]. Through, its connections, temporal lobe plays an important role in language, memory and maintaining emotional control.

The dorsolateral prefrontal cortex has extensive connections with the rest of the brain [52]. It receives afferent input from the thalamus and sends efferent output to the striatum which sends projections back to the thalamus. Involvement of this circuitry causes difficulties in integrating sensory information, poor recall, executive functions and learning [52]. The orbitofrontal cortex receives taste, smell, auditory, visual and somatosensory inputs by its connections with olfactory, inferotemporal lobe, ventral visual pathways, limbic areas, cingulate cortex, insula, striatum, as well as the dorsolateral prefrontal cortex and is related to social cognition, and its involvement may cause behavioral disinhibition [53]. The cingulate cortex has connections with the basal forebrain structures and dysfunction is associated with deficits in attention and problems with drive and motivation [52].

The cerebellum through multiple closed loop cerebro-cerebellar circuits is thought to be involved in motor control, language and social interaction [54]. Post cell therapy, PET CT scan showed an increase in the FDG uptake in these areas. It was noted that the corresponding functions also improved (Table 3).

Treatment in adulthood has a disadvantage of slower plasticity [55-57] to overcome. But, this case demonstrates the potential benefits of treatment with cell therapy using autologous BMMNCs in ID with ASD even in adulthood.

Conclusion:

As the age of the patient advances the effect of any standard treatment for ID and ASD reduces due to slower plasticity.

Also, with advancement of age the ability of the patient to learn and adapt reduces. However, intrathecal transplantation of autologous BMMNCs in this adult case of ID with ASD demonstrated significant clinical improvements without any side effects. These were affirmed by objective and imaging improvements on outcome measures such as Binet Kamath Test of Intelligence, ISAA, CARS, CGI and FDG-PET CT brain. This case study shows that BMMNC transplantation is safe and effective and may offer relief even to adults with ID and ASD who would otherwise have had to endure it throughout life.

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