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Original Research Article

PET/CT in Autism, A Diagnostic tool?

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ABSTRACT

Aims: To study areas of uptake/non uptake on PET/CT in proven cases of autism.
Methods and Material: Case series of 23 (3-26years old) pre stem cell patients with confirmed diagnosis of autism as per DSM-IV TR diagnostic criteria for autistic disorder underwent neuro PET scan after one hour of injection of 7 mCi of 18 FDG. Images were obtained on 64 slice CT and a PET system based on third generation rare earth detectors with uniform, across the field of vision resolution of 2.0 mm. Imaging data were processed using proprietary Scenium software before final image reconstruction. The SUV values of the patients were compared with normal age control with two standard deviation.
Results: 95% (22) had reduced uptake in one or both hippocampus while 82% (19) had reduced uptake in bilateral hippocampi. 82% (19) patients had low uptake in one or both amygdala while 65% (15) had low uptake in bilateral amygdala. Only 39% (9) patients had low uptake in one or both parahippocampal region while only 26 %(6) showed low uptake in bilateral parahippocampal region. 65% (15) patients had low uptake in one or both mesial temporal lobes while 52% (12) had reduced uptake in bilateral mesial temporal lobe. 56% (13) patients had low uptake in one or both cerebellum and 47 %(11) had reduced uptake in bilateral cerebellum. There was increased uptake in 74% (17) patients in one or more frontal lobes whereas 61% (14) had increased uptake in bilateral frontal lobes. Only 2 patients showed low uptake in both frontal lobes. There was increased uptake in one or both occipital lobes in 47 %(11) patients while there was 40 %(9) showing bilateral increased uptake.
Conclusions: Most patients with autism show significant low 18FDG uptake on PET imaging predominantly in hippocampus, amygdala followed by mesial temporal lobe and cerebellum while there was significant high uptake in frontal lobes.

Keywords: PET/CT, autism, autism spectrum disorder.

INTRODUCTION

Autism is the most severe form of autism spectrum disorder (ASD), while other conditions among the spectrum include mild forms known as Asperger's syndrome, childhood disintegrative disorder and pervasive developmental disorder in accordance with the criteria of fourth edition of Diagnostic and Statistical Manual (DSM-IV). It has typical characteristic features like impairment in social interaction, stereotyped repetitive behavior, and restricted interests. [1] Its prevalence is increasing world over. Studies in Asia, Europe, and North America have identified individuals with ASD with an average prevalence of about 1%. Two-thirds of ASD cases in the overall sample were in the mainstream school population, undiagnosed and untreated. [2] About 1 in 68 children have been identified with autism

spectrum disorder (ASD) according to estimates from CDC's (Centers for Disease Control and Prevention, USA) Autism and Developmental Disabilities Monitoring (ADDM) Network. ASD is reported to occur in all racial, ethnic, and socioeconomic groups. ASD is almost 5 times more common among boys (1 in 42) than among girls (1 in 189). [3] Autism has multifactorial causes including genetic and environmental factors. The exact mechanisms causing autism is poorly understood, however it is definitely related to normal neuro- cerebral development. There are multiple theories put forward leading to autism like abnormality in neural connectivity, neural migration/ activity, dendritic morphology, neuro-immune disturbances, calcium signaling etc. [4]

Neuroanatomical studies suggest that frontal lobes, mesial temporal lobe (especially amygdala) and cerebellum are also involved in the pathology of autism. There are also studies showing abnormality in blood supply or perfusion of specific areas in brain leading to this spectrum of abnormality. Hence anatomical imaging of brain and perfusion studies has been done extensively. Morphologically brain may show no abnormalities on imaging studies like CT and MRI. However PET CT can determine the uptake of cerebral blood flow and with the help of standard uptake value, areas of hypoperfusion can be quantitatively mapped. If these specific areas of low perfusion are mapped there could be focus on treatment to increase the blood flow by causing angiogenesis by drugs or stem cell therapy. This mapping will not only be helpful to confirm the clinical diagnosis but also for prognosis and post treatment follow up. [5,6]

MATERIALS AND METHODS

23 patients with clinical diagnosis of autism, pre stem cell were included in this study. All patients had confirmed diagnosis of autism according to the DSM-IV TR diagnostic criteria for autistic disorder. The youngest patient in this study was of 3 years old and oldest was of 26 years. Only two patients were adults with age being 20 years and 26 years. Mean age was 10years and median was 9 years, standard deviation being 5.5. Written consent was taken from parents and guardians of patients. This study was done over a period of 2 years.

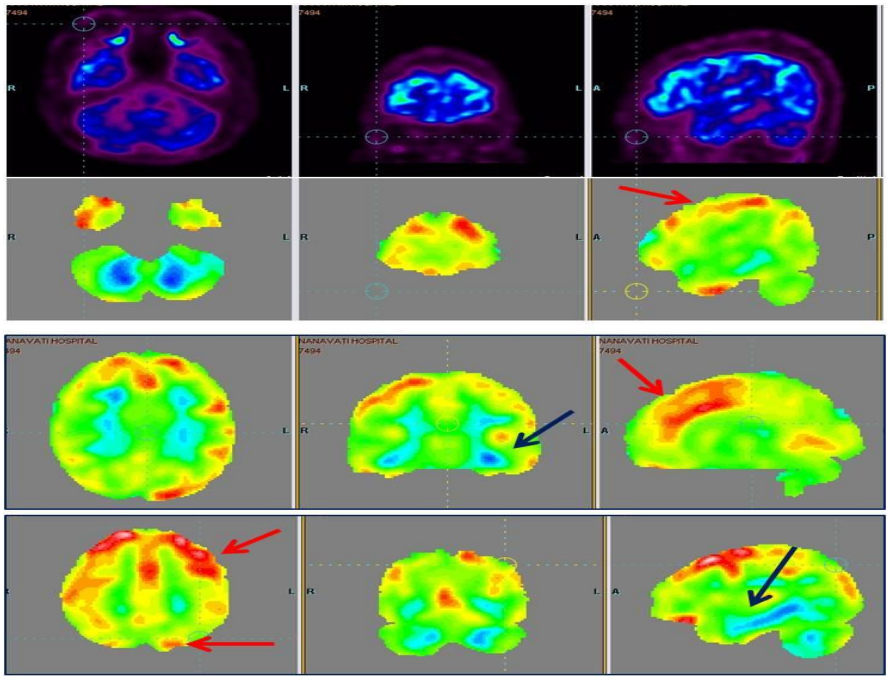

Fig1: 18FDG PET in a 16 years old boy with autism shows reduced FDG uptake (blue arrows) in mesial temporal structures like amygdala and hippocampus while increase in uptake in frontal, parietal, occipital lobes and anterior and posterior cingulate gyri.)

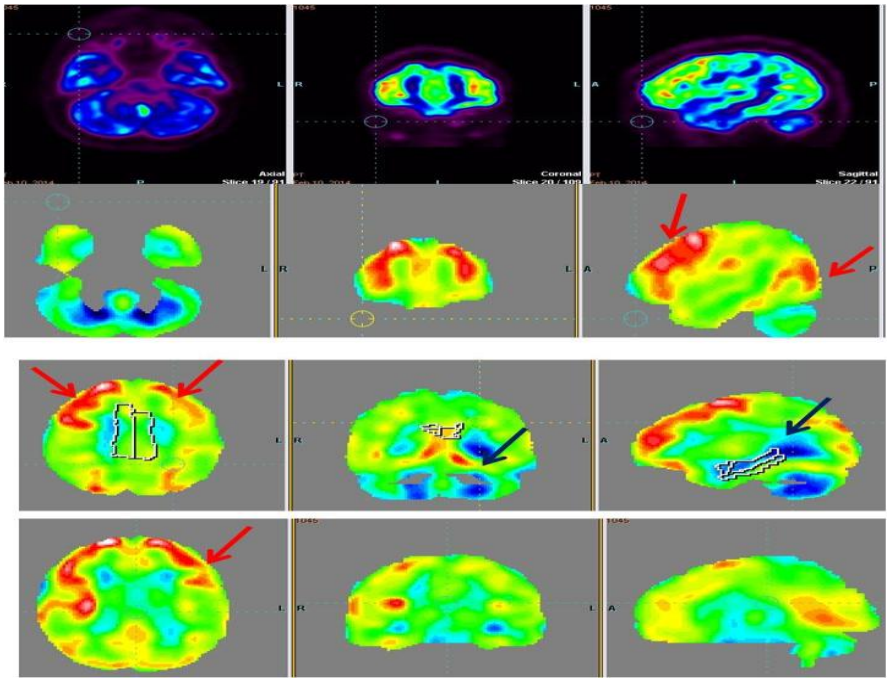

Fig2: 18FDG PET in 16 years old boy with autism shows reduced FDG uptake (blue arrows) in mesial temporal structures like amygdala, hippocampus and cerebellum while increase in uptake in frontal and occipital lobes.

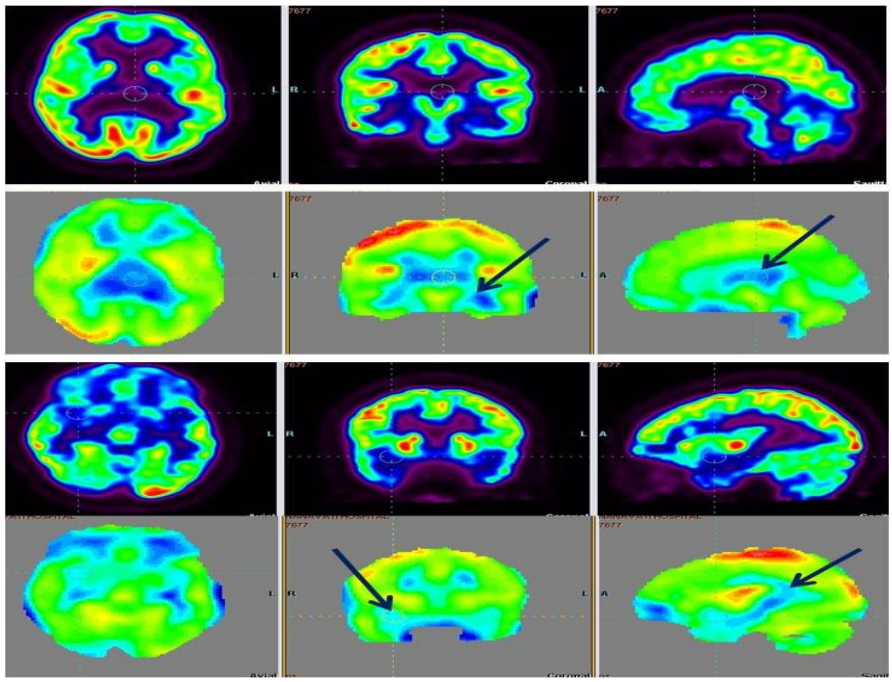

Fig3: 18FDG PET in 16 years old boy with autism shows reduced FDG uptake (blue arrows) in mesial temporal structures like amygdala and hippocampus.

These 23 patients had morphological normal brain on CT and MRI. None of the patient had history of persistent seizures or known infectious, metabolic or chromosomal abnormalities. All patients were healthy subjects and were not under any kind of drug or substance abuse. None of the patients had taken any treatment that would alter vascular dynamics or any other changes in neural mechanism. None of the patient had undergone stem cell therapy. A neuro PET scan was performed after one hour of injection of 7 mCi of ^{18}FDG. Images were obtained on 64 slice CT and a PET system based on third generation rare earth detectors with uniform, across the field of vision resolution of 2.0 mm. CT was used for attenuation correction, localization and

diagnosis. The quantitative parameter used is SUV which was measured using body weight. Imaging data were processed using proprietary Scenium software before final image reconstruction. The SUV values of the patients were compared with normal age control with two standard deviations. Deviation below -2 was considered as low uptake and above +2 as high uptake. With the help of this areas of brain were mapped showing reduced or increased uptake.

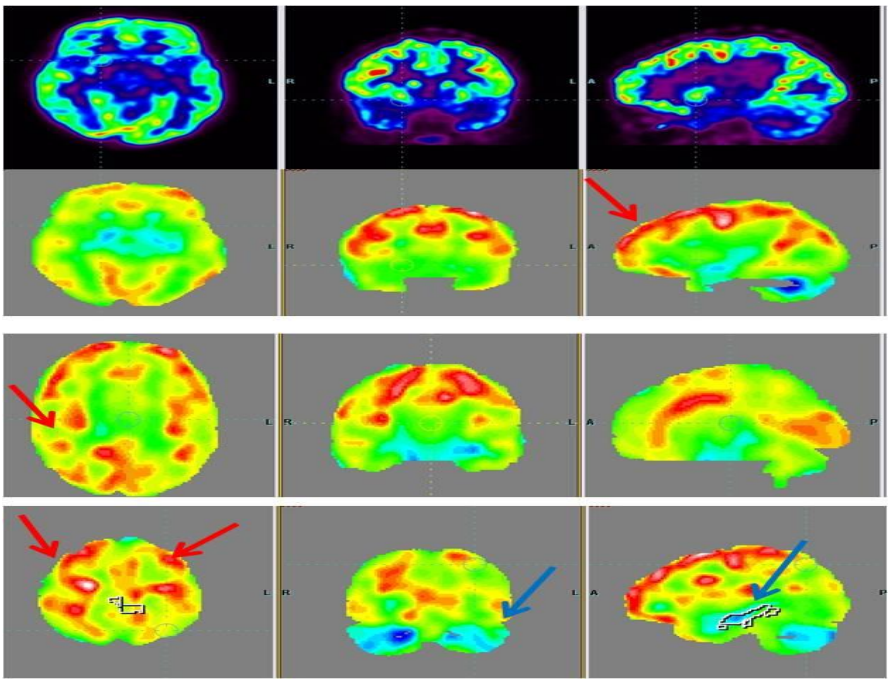

Fig4: 18FDG PET in a 8 years old boy with autism shows reduced FDG uptake (blue arrows) in mesial temporal structures like amygdala, hippocampus and cerebellum while increase in uptake in anterior, middle and posterior cingulate gyri and frontal and occipital I.

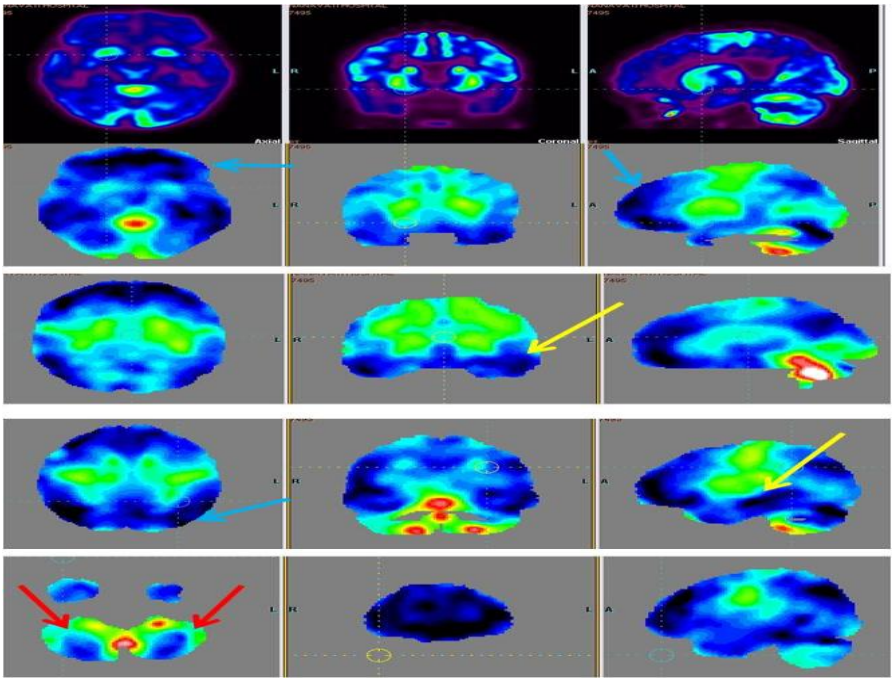

Fig 5: 18FDG PET in a 4 year old autistic boy shows reduced FDG uptake in frontal, parietal and occipital lobes (blue arrows), mesial temporal structures (yellow arrows) and cerebellum (red arrows).

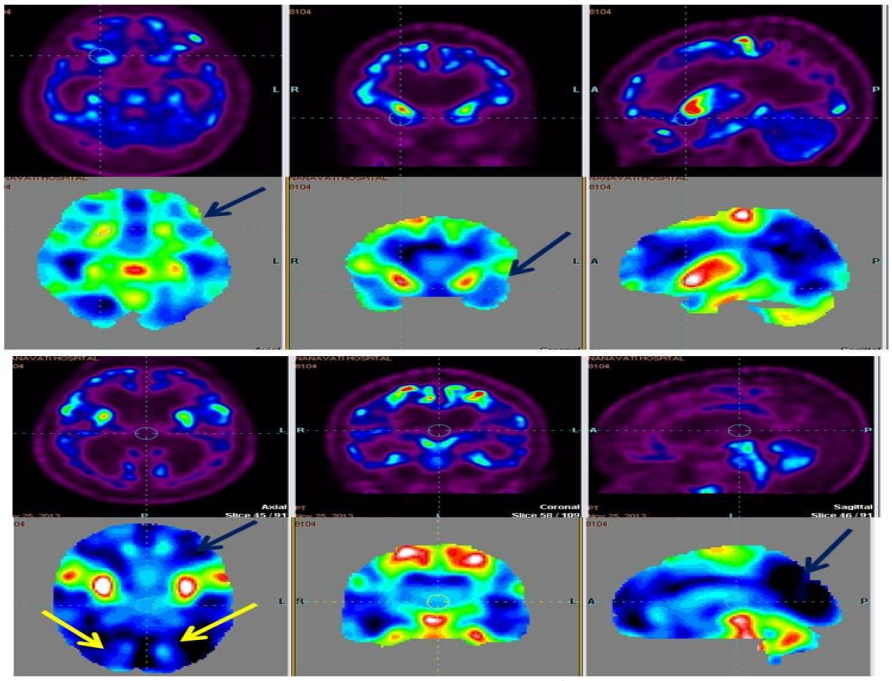

Fig 6: 18FDG PET in a 8 year old autistic girl shows reduced FDG uptake in frontal, parietal and occipital lobes (blue arrows) and cerebellum (yellow arrows).

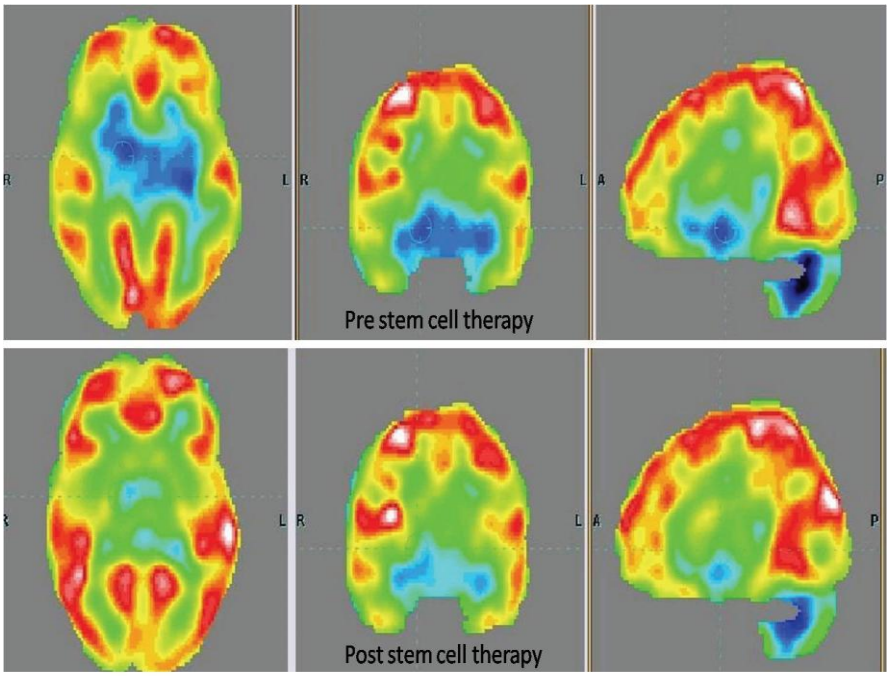

Fig 7: Sharma et al. 2013 Findings in PET-CT scan before and after cellular therapy. PET-CT scan before intervention showing reduced FDG uptake in the areas of frontal lobe, cerebellum, amygdala, hippocampus, parahippocampus, and mesial temporal lobe PET-CT scan.

RESULTS

Out of 23 patients with autism 95% (22) patients had reduced uptake in one or both hippocampus while 82% (19) patients had reduced uptake in bilateral hippocampi. 82% (19) patients had low uptake in one or both amygdala while 65% (15) patients had low uptake in bilateral amygdala. Only 39% (9) patients had low uptake in one or both parahippocampal region while only 26% (6) patients showed low uptake in bilateral parahippocampal region. 65% (15) patients had low uptake in one or both mesial temporal lobes while 52% (12) patients had reduced uptake in bilateral mesial temporal lobe. 56% (13) patients had low uptake in one or both cerebellum and 47 %(11) had reduced uptake in bilateral cerebellum.

There was no increase in uptake in hippocampus, amygdala and mesial temporal lobes on both sides. There was increased uptake in 74% (17) patients in one or more frontal lobes whereas 61% (14) had increased uptake in bilateral frontal lobes. Only 2 patients showed low uptake in both frontal lobes. Our results show that there is significantly low ^{18}FDG uptake on PET imaging in majority of patients with autism consistently seen in hippocampus and amygdala followed by mesial temporal lobe and cerebellum while there was significantly high uptake in frontal lobes.

DISCUSSION

Autism has a biological origin and understanding its pathogenesis and mechanism is a biggest challenge. The most important aim of medicine is to provide treatment for a disease but it requires reliable diagnosis. There are many studies which have provided data in structural and functional imaging of brain in cases of autism.

Back in 1985 a PET study by Rumsey et al. showed increase in metabolism and abnormalities in networking across frontal cortex, parietal cortex and subcortical regions. [7]

Critchey et al. in 2000 did a PET study showing increase in CBF in right parieto-temporal lobe, para hippocampal gyrus and in primary visual cortex which could be due to a heightened emotional status, increased processing of visual information and a more laborious engagement of cognitive functions of ASD subjects compared to normal subjects. However amygdala- hippocampal junction who is associated with processing high intellectual skills was preserved in ASD patients with high social impairment. [8]

Another study done by Rumsey in 2000 showed increase in CBF was seen in cerebellum in patients having ASD due to its firing of neuronal activity into brain stem and in system which involves emotions and higher cortical functions and skills. [9]

Pagani et al. did a study on 13 ASD patients who underwent PET CT using 1-^{11}Butanol perfusion tracer and showed significant CBF increase in right parahippocampal, posterior cingulate, primary visual and temporal cortex, putamen, caudatus, substantia nigra and cerebellum. [10]

There was significant hypoperfusion seen in bilateral temporal lobes consistently in two groups of children with autism included in study on PET CT using [15] OH2O as a tracer by Zilbovicius et al in 2000. [11]

Ohnishi et al. did a study in which 23 patients with infantile autism with control group had undergone SPECT with ^{99}Tc ethyl cystienate dimer showed decrease in rCBF in bilateral insula, superior temporal gyri and left prefrontal cortices. It also showed association of specific pattern of perfusion in limbic system and medial prefrontal cortex which are associated with social interaction and communication. [12]

In a study by Catelli, 10 adults with autism or Asperger syndrome and 10 normal volunteers were PET scanned while watching animated sequences which elicited mentalizing, in contrast to randomly moving shapes, the normal group showed increased activation in a previously identified mentalizing network (medial prefrontal cortex, superior temporal sulcus at the temporo-parietal junction and temporal poles). The autism group showed less activation than the normal group in all these regions. In the autism group extrastriate region also showed reduced functional connectivity with the superior temporal sulcus at the temporo-parietal junction, an area associated with the processing of biological motion as well as with mentalizing. This finding suggests a physiological cause for the mentalizing dysfunction in autism: a bottleneck in the interaction between higher order and lower order perceptual processes. [13]

MRI neuroanatomical study done by Hardan et al. in 2006 showed thick grey matter in temporal lobe and cerebellum

which also at the same time showed abnormal CBF in these areas. [14]

Review of literature was done by Zilbovicius et al. in 2006. It included various studies showing inconsistent findings of increase or decrease volume in vermis, corpus callosum, amygdala, cingulate gyrus and hippocampus. [6]

Anatomical MRI was done using Voxel Based Morphometry in 21 children with primary autism showed significant decrease in grey matter in bilateral superior temporal sulcus. [15]

Using functional magnetic resonance imaging (fMRI) Baron- Cohen et al. confirmed Brothers' prediction that the superior temporal gyrus and amygdala show increased activation when using social intelligence. Some areas of the prefrontal cortex also showed activation. In contrast, patients with autism or Asperger's syndrome activated the frontotemporal regions but not the amygdala when making mentalistic inferences from the eyes. These results provide support for the social brain theory of normal function, and the amygdala theory of autism. [16]

Sundaram et al did Diffusion tensor imaging in frontal lobe white matter of 50children with ASD showed abnormal fractional anisotropy (FA) and apparent diffusion co-efficient (ADC) which may be due to white matter disorganization. The fiber length distribution was significantly more positively skewed in the normal population than in the ASD group ($P < 0.001$) as the long range association fibres were significantly longer in ASD patients. [17]

There are few studies done in autistic patients using MR Spectroscopy which showed inconsistent results of decrease in NAA and myo insitol in white matter of autistic children. Researchers are also using theories of excitation and inhibition ratios in ASD and using glutamate markers on MRS to detect possible developmental defects. [18]

^{18}FDG PET CT was done in a 14 years autistic child pre and post stem cell therapy which showed before reduced FDG uptake pre intervention in areas of frontal lobe, cerebellum, amygdala, hippocampus, parahippocampus, and mesial temporal lobe. However PET-CT scan six months after intervention showed increased FDG uptake in these areas. MRI was same and showed no significant change. Child also showed clinical improvement from reduction in Childhood Autism Rating Scale (CARS) from 43.5 (severely autistic) to 23.5 (non-autistic). [19]

CONCLUSION

Multiple modalities of radiology and nuclear medicine have used to study anatomy and functioning of various anatomical regions of brain. However, there are inconsistent results overall. Our study however, showed consistent findings of significant low uptake in hippocampus, amygdala, mesial temporal lobe and cerebellum along with significant high uptake in frontal lobes in patients with autism. More studies with control group are required to come to conclusion.

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