Preliminary evaluation of ^{18}FDG PET findings in pediatric patients with autism

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Summary

Objective: The purpose of this study was to evaluate ^{18}FDG positron emission tomography (PET) findings in pediatric patients with autism. *Subject and method*: This study includes 15 autism pediatric patients who were diagnosed at the Vinmec International Hospital from January 2017 to May 2017 and five oncology patients without neurology's diseases underwent to whole body PET scan (from vertex to midthigh) were selected as control group. All patients underwent PET/CT brain examination in Nuclear Medicine Department, 108 Military Central Hospital. *Result:* Mean patient age (7.1 ± 0.24). On the PET scans of the 15 patients with autism, 13 (86%) had significantly decreased metabolic activity of both hemispheres. All of the patients had decreased metabolism in temporal, parietal and cingulate gyrus. Mean of Z-scores of autism group showed significantly decreased activity in comparison with Z-score of the control group. There were relations between clinical and grade of hypometabolism of autism. *Conclusion:* Hypometabolism in the brain of autism pediatric patients may present a role in diagnosis and prognosis.

Keywords: Autism, ^{18}FDG PET.

1. Background

Among the form of autism spectrum disorder (ASD), autism is the most severe disease, while other include mild forms known as Asperger's syndrome in the criteria of the fourth edition of Diagnostic and Statistical Manual (DSM IV). Autism has typical clinical characteristic features as impairment in social interaction, stereotyped repetitive behavior, and restricted interests. The number of prevalence has increased globally, some studies have identified individuals with ASD with an average prevalence of about 1% and two-thirds of the cases in the mainstream school's age [6].

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The pathophysiology of autism is unclear however, it may relate to the neuro-cerebral development. According to multiple theories, the leading causes of autism could be the abnormalities in neural connectivity, neural migration/ activity, dendritic morphology, neuro-immune disturbances, calcium signaling and etc. Several studies presumed that frontal lobes, mesial temporal lobe and cerebellum are involved in the pathology of autism. Other studies suggest that abnormality in perfusion of specific areas in brain leading to this spectrum of autism. Hence, anatomical and fusion imaging of brain has been recommended for diagnostic of autism. Nevertheless, rarely the abnormalities of the morphological brain were detected by conventional diagnostic imaging like CT and or MRI. Positron emission tomography-computed tomography (PET/CT) can determine the

metabolic uptake of cerebral blood flow and the regions of hypoperfusion and hypometabolism could be quantitatively assessed. This mapping of hypometabolism may not only be the complimentary to confirm the clinical diagnosis but also for prognosis and treatment's follow up.

The studies by Chugani el al that prospectively followed children with infantile spasms has linked bilateral temporal hypometabolism with the development of autism [5]. Chivate el al published that 95% patient had reduced uptake in one or both hippocampus while 82% had reduced uptake in one or both amygdala [2]. To our best knowledge, there not any study in Vietnam was report F-^{18}FDG PET findings in pediatric patients with autism. Therefore, we carry out this research to evaluate PET findings in children with autistic features in this cross-sectional study.

2. Subject and method

Study participants were include group of autism and control group. Controls were five pediatric patients with diagnosis of lymphoma without any neurology's abnormalities underwent to whole body PET/CT scan. Then normal data of PET/CT brain was reconstructed. The fifth teen autism patients were recruited from the Pediatric Department, Vinmec Hospital. The Autism Behaviour Checklist (ABC), the Childhood Autism Rating Scale (CARS) and DSM IV diagnostic criteria for autism spectrum disorders were administered by a trained clinician [1]. The patients with infection diseases and disagree enter to study were excluded.

The PET/CT brain protocol for pediatric patients was followed by EANM procedure guidelines for PET brain imaging using ^{18}FDG, version 2. Patients should fast for at least 6 hour to allow optimal cerebral FDG uptake not influenced by increased serum glucose levels. ^{18}FDG would be injected for patient if the blood glucose's level lower than 8.8mmol/l. The ativity of ^{18}F-FDG was calculated by EANM dosage card v.1.5.2008, 3-D is recommended especially in children [7]. All patients was sedated by propofol (2mg/kg) parenterally and afterward PET/CT brain scan was performed after injection of ^{18}FDG 60 minutes. PET scans were performed during sleep and the vital signs of the patients, as well as eye, head and body movements, were monitored firstly, patient was scanned scout and low dose CT with 130kV, 80 - 120mAs, 2.5mm/slice, pitch: 1.6. The PET brain scan was recorded in one bed position in 5 minutes. The CT image was reconstructed by filtered back projection and PET image in iterative reconstruction (3D), attenuation correction was done by CT. The PET/CT images were analyzed by nuclear physician on Cortex ID software, GE Medical Systems. Quantitative assessment bases on Z-score using 3D-SSP mapping.

The PET findings for the patients with autism and the control group were evaluated using the Statistical Package for the Social Sciences version 13.0 for Windows (SPSS, Chicago, IL, USA). When comparing the data, the Student's t - test was used for normally distributed continuous variables, the Mann-Whitney U-test for abnormally distributed continuous variables and the Chi-squared test for categorical variables, while Fisher's exact test was used whenever the expected value was < 5. A $p<0.05$ was considered significant.

3. Result

Table 1. General characteristics of autism patients

	n		p
Age	7.1 ± 3.02 (minimum: 2, maximum: 14)		
Gender	Female 12 (75%)	Male 3 (25%)	
History of epilepsy	3 (20%)		
Mild mental retardation	3		

Moderate mental retardation	7		
Severe mental retardation	5		
Activity of ^{18}FDG (mCi)	4.4 ± 1.05		
Glucose metabolism	Hypometabolism 13 (86%)	Normal metabolism 2 (14%)	=0.02
Z-score (mean ± SD)	-1.6 ± 0.66	2.06 ± 0.56	

There are 3 of 15 (20%) patients have history of epilepsy. The age of patient is variable (the lowest is 2 years old, the highest is fourteen years old), mean age 7.1 ± 3.02. The age of female patient is 7 ± 4.58 higher than 7.1 ± 2.79 of male patient but there is no statistic difference (p=0.92). The mean activity of ^{18}FDG is 4.4 ± 1.05 (minimum is 4mCi, maximum is 7mCi). Metabolism of ^{18}FDG was decrease in both hemisphere in 13 of 15 patients (86%), two patient (14%) have normal glucose metabolism. Z-score mean of both hemisphere of autism is significant lower than that of control group (p=0.02).

Table 2. The characteristic of ^{18}FDG metabolism in control group

Number	5	
Age	Mean: 8 ± 4.22 (min: 4, max: 18)	
Gender	Male 3 (60%)	Female 2 (40%)
Activity of ^{18} FDG (mean ± SD)	4.1 ± 3.02	
Z-score (mean ± SD)	2.15 ± 0.56	

There was no abnormalities of ^{18}FDG metabolism, Z-score mean: 2.15 ± 0.56.

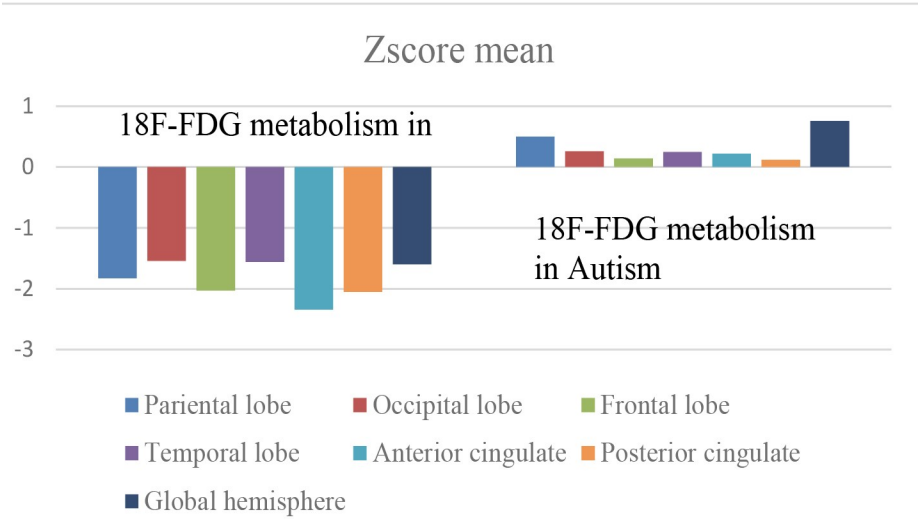

Figure 1. Z-score in autism and control group

Z-score (mean mean ± SD) in all cortex regions of both hemisphere is lower than that of control group. The difference is statically significant between Z-score mean of autisms and controls (p<0.05).

Table 3. Qualitative and quantitative ^{18}FDG metabolism of brain cortex

Regions	Light (n)	Fit (n)	Heavy (n)	Total (n)	Z-score	p
Right parietal lobe	1	4	8	13	-1.9 ± 1.65	0.03

Left parietal lobe	2	4	7	13	-1.6 ± 1.75	
Right occipital lobe	1	6	5	12	-1.5 ± 1.61	0.01
Left occipital lobe	2	5	6	13	-1.2 ± 1.56	
Right frontal lobe	1	5	7	13	-1.7 ± 1.5	0.037
Left frontal lobe	2	5	6	13	-1.6 ± 1.5	
Right temporal lobe	1	6	5	12	-1.5 ± 1.76	0.005
Left temporal lobe	2	8	2	12	-1.98 ± 1.64	

Table 3. Qualitative and quantitative ^{18}FDG metabolism of brain cortex *(Next)*

Regions	Light (n)	Fit (n)	Heavy (n)	Total (n)	Z-score	p
Right anterior cingulate	2	6	5	13	-1.5 ± 1.25	0.03
Left anterior cingulate	2	8	3	13	-1.02 ± 1.23	
Right posterior cingulate	2	9	1	12	-1.53 ± 1.25	0.16
Left posterior cingulate	2	8	2	12	-1.29 ± 1.21	
Right cerebellum	5	1		6	-0.39 ± 0.82	0.937
Left cerebellum	5	2		7	-0.38 ± 0.75	
Total	***27***	***76***	***64***	***167***		

All 13 autism patient with decrease ^{18}F-FDG metabolism showed decrease bilaterally glucose metabolism in parietal, frontal lobe and cingulate gyri. Twelve of third teen patients (92%) had decrease glucose metabolism in all remained regions of cortex. Regarding to the level of decrease glucose metabolism, serve decrease metabolism was seen in 38% patient (64/167 regions), moderate decrease metabolism was 45% (76/167 regions) and mild decrease metabolism was 17% (27/167 regions). Quantitative analyze indicated that Z-score mean in the right hemisphere cortex regions was higher than left hemisphere ($p<0.05$). Most of cortex regions have decrease ^{18}F-FDG in mild and moderate level. There was no significant difference in metabolism between both cerebellum ($p=0.937$).

Table 4. Quantative and quantitative glucose metabolism in functional region on the cortex brain in autism

Region	Mild (n)	Moderate (n)	Severe (n)	Total (n)	Z-score	p
Right Sensorimotor	1	4	8	13	-1.9 ± 1.65	0.03
Left Sensorimotor	2	4	7	13	-1.6 ± 1.75	
Right visual cortex	1	6	5	12	-1.5 ± 1.61	0.01
Left visual cortex	2	5	6	13	-1.2 ± 1.56	
Right caudate	1	5	7	13	-1.7 ± 1.5	0.037
Left caudate	2	5	6	13	-1.6 ± 1.5	
Total	***9***	***29***	***39***			

The hypometabolism of all functional region on the cortex was seen in all autistic patients with moderate and severe level. Z-score of the regions on the right hemisphere are higher than that on the left ($p<0.05$).

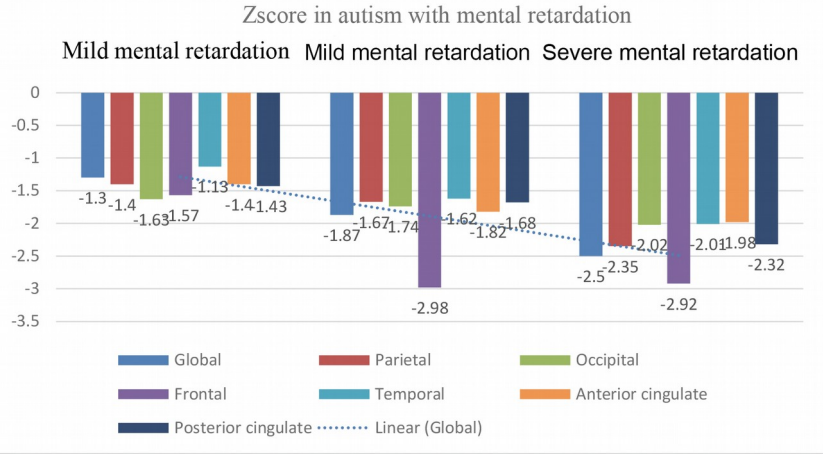

Figure 2. Comparing Z-score mean in autism related to mental retardation

The significant difference of Z-score mean in the autisms have mild, moderate and severe mental retardation was recorded ($p<0.05$).

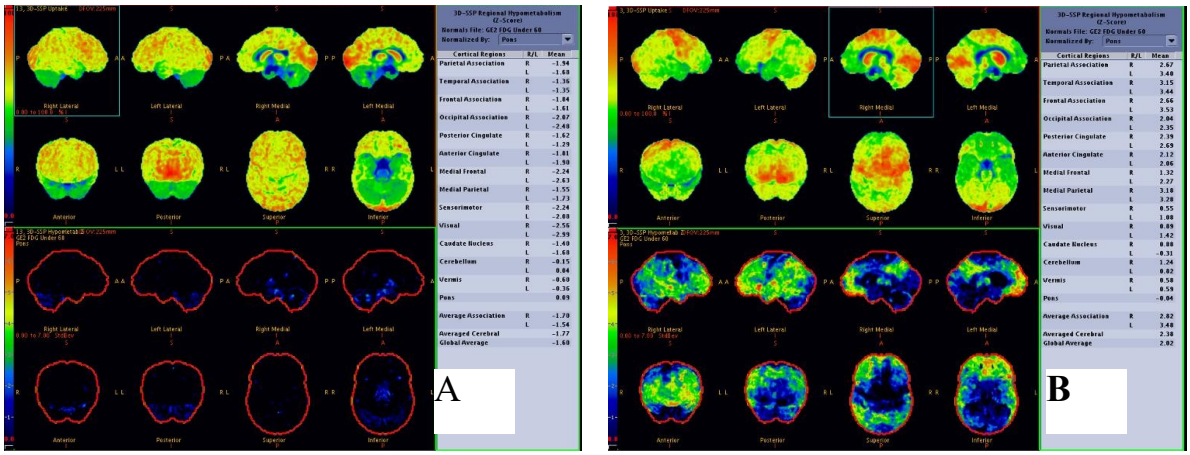

Figure 3. A: ^{18}FDG metabolism of cortex is normal in control.
B: Decrease metabolism of ^{18}FDG bilaterally on the frontal, occipital, temporal, hippocampus and anterior cingulate in autism

4. Discussion

To our the best knowledge, all studies assessing glucose metabolism behalf on PET/CT imaging showed the hypometabolism in some of brain cortex regions. In our research, 86% patients have decrease ^{18}FDG metabolism which is similar to the result published by Rahul et al [2]. However, several studies using PET without CT and computed assistance illustrated the hypermetabolism of glucose in occipital, parietal and temporal lobe. The hypermetabolism of ^{18}FDG on brain of children autism was seen in some studies maybe due to the speech test was performed before undergoing to PET scan. The previous studies applying PET without CT indicated the variable patterns of ^{18}FDG metabolism. However, recent papers pubished by Dilber et al and Mitleman et al depicted hypometabolism on brain cortex of more than 90% of autisms [3], [9]. PET intergrated with CT and 3D-SSP mapping with normal data improve the image quality of brain so that the later studies may show more reliable results. In fact, the pathophysiology of autism is still much debate and the glucose metabolism of autism patients could not be a specific diagnosis. The

hypometabolism of ^{18}FDG in autism maybe due to the abnormality of neural connectivity in frontal, mesial temporal lobe (espesially amygdala).

The difference of brain glucose metabolism in 18 children with autism and controls are significant. Quantitatively assess glucose metabolism of whole brain and focal area, Z-score in autism is bilateral decrease in comparison with controls. Mitleman et al reported that the brain of autism and schizophrenia group showed similar changes in metabolic rates for example the hypometabolic changes were obtained in the frontal, parietal, hippocampus and thalamus. However, the opposite changes were found in control groups. The reason could be explain that this functional regions related to the centers of speech and communication. The hypometabolism detected on PET imaging correlated with the disorder of behaviors in autism. The significant bilateral temporal hypoperfusion centered in the associative auditory cortex and the multimodal temporal cortex was also found in previous study [8]. The temporal lobe has a crucial role in processing of various environmental signals and organizing them into experiences that confer meaning to the world around us. Auditory cortex dysfunction may explain why young patients with autism are often initially misdiagnosed as deaf and why they often have severe communication impairments, while superior temporal sulcus dysfunction may indirectly account for the emotional and cognitive aspects of autism. On fMRI images the sub cortical centers showing abnormality however, hypo metabolism only was seen on amygdala.

Review of literature was done by Zilbovicius et al in 2006 [10]. It included various studies showing inconsistent findings of increase or decrease volume in vermis, corpus callosum, amygdala, cingulate gyrus and hippocampus. 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. In addition, beside the cortex, subcortical center such as visual, sensorimotor, putamen and amygdala showed hypometabolism of FDG in almost autims. However, the severe hypometabolism level mostly seen on frontal, temporal lobe, anterior cingulate. The study was done without CT may not detect the abnormality on cerebellum. In contrast, our study showed decrease mildly decrease metabolism due to the high resolution of PET/CT.

In a study where a small group of patients with autism and mental retardation was examined using single photon emission CT scans reported hypoperfusion particularly in the frontal and prefrontal areas [4]. In another study, the correlation was significant between ^{18}FDG metabolism of autism and mental retardation which is similar to our study [3].

5. Conclusion

There is the significant difference between metabolism of autism and control's group. The severe, moderate and mild hypometabolism was seen on occipital, parietal, temporal, cingulate and subcortical centers. The metabolism among autism and mental retardation were related to each other.

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