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Case Report

Disease Progression in Early Onset Alzheimer's Dementia Over a Period of 1 Year using ^{18}F-FDG-PET – A Case Based Approach

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Abstract

Alzheimer's Dementia (AD) is a progressive neurodegenerative disorder and is one of the most common causes of dementia in older adults. The pathology of AD is characterized by intracellular neurofibrillary tangles and amyloid plaques in the extracellular space. Herein, we describe a case of a 51-year-old woman who complained of behavioural changes and memory loss which led to a diagnosis suggestive of dementia.^{18}F-FDG-PET brain scan was performed to evaluate and study the pathological changes and confirm the diagnosis. It showed hypometabolism in precuneus, posterior cingulate cortex, angular gyrus, supramarginal gyrus and medial temporal cortex. A diagnosis of young onset dementia was made. Over next one year, despite standard treatment there was rapid progression of dementia. A battery of tests was performed which included mini mental state examination (MMSE), Addenbrooke's Cognitive Examination (ACE), biochemical tests, 2D Echocardiography and color Doppler study. On MMSE she scored 10 while on ACE she scored 42. The repeat ^{18}F-FDG-PET scan showed severe deterioration in brain glucose metabolism indicating an accelerated progression of early onset AD. This also correlated with deterioration in patient's clinical symptoms. This is a unique case as it describes the use of ^{18}F-FDG-PET as an early biomarker for diagnosis of early onset AD and demonstrates the rapid progression of brain pathology in early onset AD. This case highlights the importance of diagnosis of AD in its initial stages which will facilitate better management.

Keywords: *Alzheimer's Dementia; Early Onset Alzheimer's Dementia; 18F-FDG-PET; Young Onset Dementia*

Introduction

Alzheimer's Dementia (AD) is a progressive neurodegenerative disorder due to the gradual accumulation of abnormal proteins (Amyloid- B and phosphorylated tau) in the brain, which leads to synaptic, neuronal and structural damage. The onset of AD is characterized by severe decline in episodic memory. At the cellular level, it is characterized by progressive loss of neurons especially pyramidal cells which mediate the cognitive functions [1,2]. Different studies suggest that dysfunction of the synapse during the early phase of the disease disturbs communication within the neural circuitry [3]. The pathology of AD starts with degeneration of medial temporal cortex especially in entorhinal cortex and the hippocampus, further spreading across the temporal and parietal association cortex [4]. This deterioration in neuronal circuits lead to impairment in memory, learning, language, reasoning, executive functions and visuospatial functions affecting the quality of life of the patient.

Multiple studies have shown that the degenerative changes in AD commence decades before the clinical manifestation [5,6]. The onset of symptoms before the age of 65 years is defined as early onset AD. The cases of early onset AD are either familial or sporadic and represent about 10% of all AD cases [7]. Early onset AD clinically manifests with non-amnestic symptoms in 25 - 65% cases and presents

with aphasia, apraxia and visuospatial functional deficits [8,9]. Recent studies have shown that amyloid markers (cerebrospinal fluid amyloid-β_{42} and PET amyloid tracer uptake) might represent the earliest detectable changes in AD. Functional and metabolic markers detected by fMRI and ^{18}F-fluorodeoxyglucose PET are abnormal after the amyloid markers. These amyloid markers are detected during the early asymptomatic course of AD, and continue to change well into the dementia stage. Structural changes come later, starting with entorhinal cortical atrophy, followed by hippocampal and temporal cortical atrophy and finally resulting in whole brain atrophy [10]. Early onset AD patients show atypical neuropsychological symptoms along with structural and functional changes in neuroimaging studies. Currently, there are no available radiological tests for the definitive diagnosis of early onset AD. However, magnetic resonance imaging (MRI) is used to assess structural tissue changes (atrophy) and ^{18}F-FDG-PET is used to measure functional changes. To slow down the progression, it is essential to detect the disease at an earlier stage which will also result in maximal outcome of the treatment. Active research is being conducted to establish techniques such as functional MRI (fMRI), resting state fMRI Amyloid tracers for PET, which may help assist the current methods with the early diagnosis of AD.

Herein, we describe a case of a 51-year-old female patient clinically diagnosed as young onset dementia. This is one of the few cases of early onset AD in which rapid progression of brain pathology was studied over a period of one year using ^{18}F-FDG-PET as a biomarker.

Case Presentation

A 51-year-old female with history of severe memory loss was assessed as an outpatient. As she was unable to provide her detailed history; the admitting physician relied on her husband and family for the information. At the age of 46, the patient started displaying sudden mood swings followed by aggressive and hyperactive behaviour. By 48 years, the symptoms progressed to numbness of fingers followed by memory loss as reported by the husband. The patient was prescribed medications to control the mood swings and was diagnosed as young onset dementia by a psychiatrist. There was no familial history of dementia. At the age of 50, she underwent ^{18}F-FDG-PET which revealed hypometabolic observations in precuneus, posterior cingulate cortex, angular gyrus, supramarginal gyrus and medial temporal cortex. An asymmetrical pattern was observed in the patient where the left hemisphere was more severely impaired as compared to the right hemisphere of the brain as shown in figure 1 and 2.

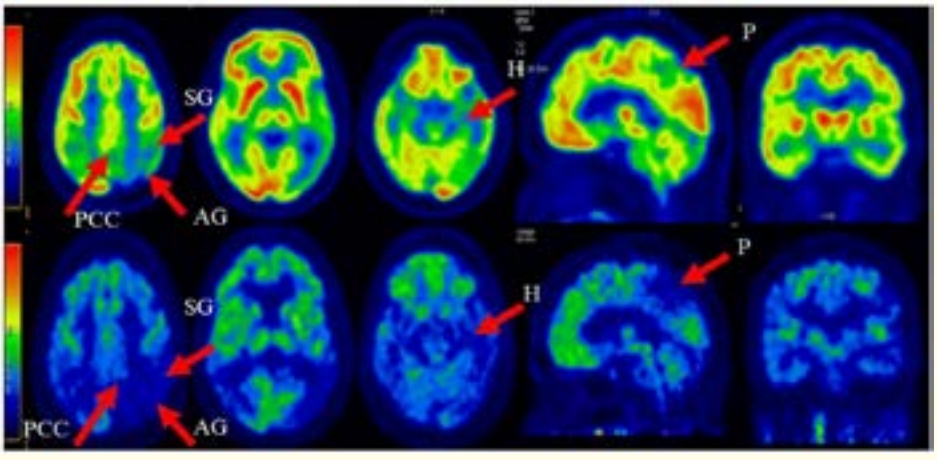

Figure 1: *Transaxial, coronal and sagittal images of a 51-year-old woman diagnosed as early onset Alzheimer's disease. Asymmetry is observed in posterior cingulate, precuneus along with metabolic reduction of few surrounding cortices of left parietal lobe. The above image show 18F-FDG-PET scan performed during 2015 and below image show 18F-FDG-PET scan performed during 2016. The arrow head indicates the region of interests, PCC: Posterior Cingulate Cortex; AG: Angular Gyrus; SG: Supramarginal Gyrus; H: Hippocampus; P: Precuneus.*

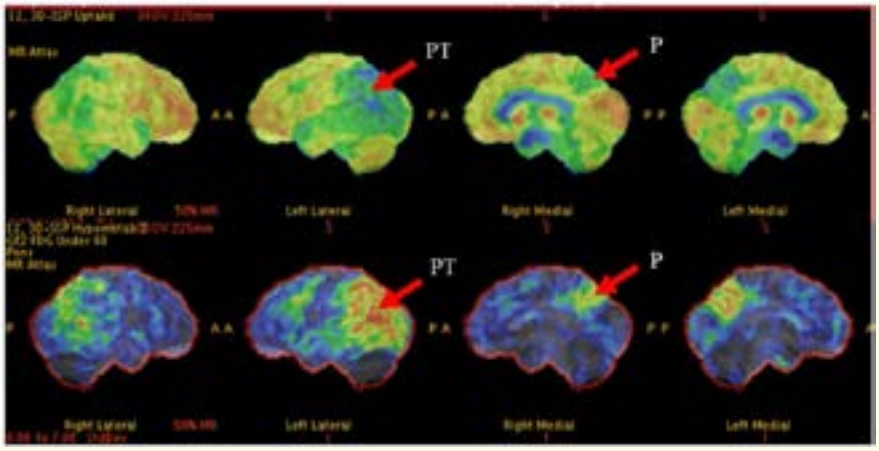

Figure 2: *Three-Dimensional stereotactic surface projection (3D-SSP) maps of a 51-year-old women during 2015. 3D-SSP maps show hypometabolism in both parietotemporal association cortex. The arrow head indicates the region of interests, PT; Parietotemporal Association Cortex; P; Precuneus.*

Over a period of one year there was rapid deterioration in her cognition, memory and behaviour. Disorientation to time and place, completely forgetting how to cook, forgetting names of familiar people and difficulty in having meaningful conversations was observed. Patient also had difficulty in purchasing things from a shop and handling money. She could not travel on her own and was completely dependent for her activities of daily living (ADL). She underwent a battery of examinations including mini mental state examination (MMSE), Addenbrooke's Cognitive Examination (ACE), 18F-FDG-PET, Biochemical tests, 2D Echocardiography and color Doppler study.

^{18}F-FDG-PET scan was performed to study the progression and severity of the disease pathology over one year. Both ^{18}F-FDG-PET scans were performed in the same GE Discovery IQ PET/CT scanner with 5-Ring. In comparison with the first ^{18}F-FDG-PET scan, the scan done after one year showed progressive hypometabolism in parietotemporal association cortices (Figure 3). The mean Z score ($Z = [mean_{subject} - mean_{database}]/S_{Ddatabase}$) was calculated voxel by voxel with a threshold of $P \leq 0.01$ (1-sided) corresponding to $Z \geq 2.33$ [11,12]. Three-dimensional stereotactic surface projections (3D-SSPs) of the Z scores were generated to determine the metabolic abnormalities. Z scores were calculated for the patient in 2015 and 2016 (Table 1). Higher Z score indicated reduced FDG uptake. The findings showed rapid progression of pathology in our patient.

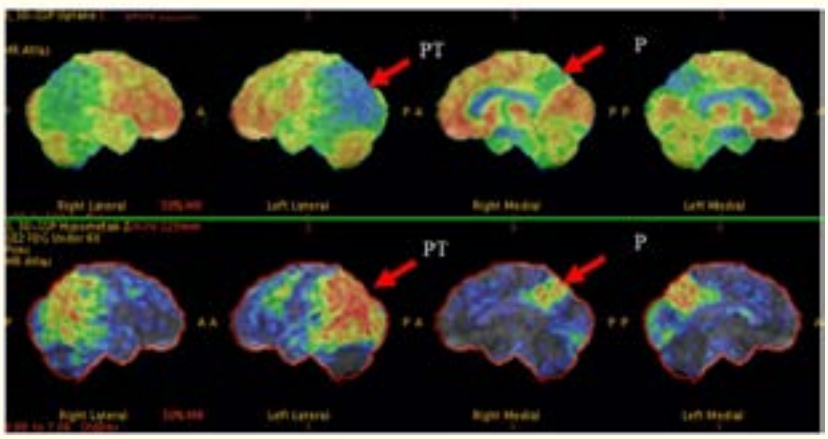

Figure 3: *Three-Dimensional stereotactic surface projection (3D-SSP) maps of a 51-year-old women during 2016. 3D-SSP maps show severe hypometabolism in both parietotemporal association cortex. The arrow head indicates the region of interests, PT: Parietotemporal Association Cortex; P: Precuneus.*

Cortical Regions		2015	2016
Parietal cortex	R	3.46	4.66
	L	4.92	5.67
Temporal cortex	R	1.89	2.65
	L	2.83	3.46
Frontal cortex	R	0.93	0.77
	L	1.76	1.51
Posterior cingulate	R	1.59	1.7
	L	2.24	2.59
Anterior cingulate	R	1.11	0.25
	L	1.31	0.58
Medial frontal	R	0.72	0.16
	L	0.93	0.24
Medial parietal	R	3.27	3.56
	L	4.16	4.81
Sensorimotor	R	0.93	0.74
	L	0.87	1.2
Visual cortex	R	0.89	1.38
	L	1.92	2.61
Caudate nucleus	R	-0.22	-0.13
	L	0.93	0.4
Cerebellum	R	0.6	1.21
	L	0.11	0.14
Vermis	R	0.63	0.76
	L	0.53	0.6
Pons		0.05	0.17
Average association	R	1.6	1.93
	L	2.56	2.73
Averaged cerebral		1.73	1.74
Global Average		1.44	1.45

Table 1: Z score of the patient during 2015 and 2016.
Abbreviations: L: Left; R: Right

Neuropsychological examination

The patient was evaluated on two global cognitive screenings which included the Mini Mental Status Examination (MMSE) and the Addenbrooke's Cognitive Examination (ACE) as shown in table 2 and 3. The scores obtained were interpreted on the basis of normative data for the Indian population [13].

Domains	Scores
Orientation	3/10
Attention/Concentration	
Registration	2/3
Serial Subtraction: 100-7	0/5
Memory	
Anterograde 3 word recall	1/3
Language	
Naming (watch, pencil)	2/2
Comprehension (Reading instruction)	1/1
Comprehension – 3 stage	0/3
Repetition (Phrases)	1/1
Writing	0/1
Visuospatial Functioning	
Copy – Overlapping Pentagons	0/1
Total	10/30

Table 2: *Mini Mental Status Examination (MMSE).*

Domains	Scores	NORMS- Mean and S.D (As per age education level)
Orientation	3/10	7.3 to 8.5
Attention	0/5	4.1 to 5.5
Registration	14/24	16.9 to 23.3
Recall	1/10	5.3 to 9.1
Remote Memory	1/4	3.4 to 4.2
Verbal Fluency	4/14	5.2 to 12.6
Naming	7/12	8.6 to 13
Language	11/16	14.8 to 16.6
Visual spatial	1/4	2.2 to 5.4
Total	42/100	76.2 to 90.6

Table 3: *Addenbrooke's Cognitive Examination (ACE).*

Mini Mental Status Examination (MMSE)

MMSE is a questionnaire extensively used in clinical setting to measure cognitive impairment of the dementia patients. On MMSE, the patient scored 10/30 (Mean Average Range = 25.44 to 30.8 and Standard Deviation of 2.4) indicating significant cognitive impairment.

Addenbrooke's Cognitive Examination (ACE)

The ACE is a screening battery similar to MMSE but in addition it includes a detailed examination of memory (seven items address with delayed recall), language (naming, comprehension, reading, writing) and visual-spatial parameters (two copy designs and clock drawing) and also has items for assessing executive functioning (verbal fluency) of the patient. Patient scored 42/100 in ACE indicating significant global cognitive impairment.

On biochemical analysis, patient showed elevated SGOT and SGPT in hepatic profile. Normal 2D- Echocardiography showed normal chamber size with no regional wall motion abnormality at rest. Presence of Type 1 diastolic dysfunction with mild pulmonary hypertension and no pericardial effusion. Following different neuropsychological examination including MMSE and ACE, the patient was diagnosed with probable or possible AD using National Institute for Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) guidelines [14].

Discussion

It's been a century since the German psychiatrist and neuropathologist Alois Alzheimer described the first case of AD. Since then, there has been a significant progress in understanding the pathology, diagnosis and treatment of AD. It is the most common type of dementia in adults which accounts for 50 - 60% of cases of dementia [15]. As the life expectancy period is increasing, the number of people with dementia is also expected to grow from 35 million to 65 million by 2030 [16]. However, the high prevalence of dementia in the older patients overshadow its occurrence in the younger population [17]. Population below 65 years of age is conventionally included in the category of young onset dementia. Even though diagnosis of dementia in younger patients appears challenging, early onset can be treated to slow down the disease progression.

A definitive diagnosis of AD, is currently only possible by post-mortem histopathological analysis of the brain. Amyloid plaques and neurofibrillary tangles (NFT) are the pathological hallmarks of AD lesion which follows a stereotypical pattern of spread of pathology along the neocortex regions [18]. The amyloid plaques are extracellular accumulation of amyloid protein and consist of insoluble amyloid beta protein, while NFTs are intracellular aggregates of abnormal hyper phosphorylation of tau protein [19-21]. As the incidence of AD is increasing rapidly, the development of novel treatments to delay disease onset or progression is crucial. For maximal benefit of treatment and to maintain the functions and quality of life of the patients with AD, an early diagnosis is essential. Clinical features like poor episodic memory are consistent with early AD however, they overlap with other cognitive impairments making the diagnosis of AD difficult based only on clinical symptoms. Functional neuroimaging techniques combined with neuropsychiatric examination, neurocognitive testing, clinical features and structural neuroimaging, may help in confirming the early onset of AD.

In this case report, we have emphasized the use of Brain ^{18}F-FDG-PET for early detection of AD. ^{18}F-FDG-PET measures the synaptic activity in the brain. As, glucose is the source of energy for brain, glucose analogue ^{18}F-FDG-PET is a suitable indicator for measuring brain metabolism. Additionally, during resting state, brain's energy is largely maintained by glutamatergic synaptic signaling and ^{18}F-FDG uptake strongly correlates at autopsy with the levels of synaptic vesicle protein synaptophysin [22,23]. This makes ^{18}F-FDG-PET as a valid biomarker for measuring synaptic activity. Hence it has been widely used in marking up the early stages of the AD, having a sensitivity of 90% and providing effective quantitative and topographical correlation with clinical progression [24]. However, ^{18}F-FDG-PET has certain limitations when used to diagnose AD such as specificity for AD pathology. Hence in the future amyloid tracers specific to AD might be a useful addition for early diagnosis of AD [25].

In this case report, we describe 1-year clinical follow-up of a 51-year-old woman who came to us with a diagnosis of young onset dementia, but later diagnosed as early onset AD based on ^{18}F-FDG-PET findings. Previous studies conducted in AD patients have shown hemispherical asymmetries along with hypometabolism in the parietal region, posterior cingulate cortex (PCC) and precuneus [11,26]. These are considered as hallmark for AD pathology. These metabolic abnormalities were also seen in the present case. Also, severe hypometabolism in the parietal and PCC indicates rapid deterioration in early onset as compared to late onset of AD [6].

During the clinical follow-up of 1 year, the patient showed fast decline in metabolism of posterior cingulate cortex, precuneus, hippocampus and other associated regions of AD which correlated with the severe impairment in cognition and memory. The severe deterioration in metabolism corresponds to the disease severity and is also associated with the reduced score in cognitive tests [26,27].

Early diagnosis gives the family an opportunity to know about the pathogenesis, cognitive changes, develop realistic expectations and plan for future concerns. It allows the individual to learn strategies and tips for better management of the disease. It also helps in legal, financial and long-term care planning. Moreover, early detection can help individuals avail the advantage of clinical trials, improved care, delaying the progression, effective treatment planning and achieve optimum benefits of the treatment.

The present case brings to notice that in young onset dementia, one should look for AD related hallmark features to diagnose as early onset AD. Also, it highlights the utility of 18F-FDG-PET as an effective method to determine the disease progression.

Conclusion

^{18}F-FDG-PET is a valuable tool in diagnosing early onset AD and monitoring disease progression. Moreover, the present case highlights the rapid progression in early onset AD. Hence, a timely diagnosis is essential in the management of early onset AD.

Conflict of Interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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