Mitigating the Dilemma in Dementia: A Case Series of the First Amyloid Brain PET scans in the Philippines

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ABSTRACT

Diagnosis of Alzheimer dementia is done clinically using criteria set by different neurological associations. Inevitably, clinicians encounter cases that do not fulfill the set definitions and have to resort to supporting data to form a clinical judgment. Part of the ancillary work-up for dementia is the brain amyloid PET scan that has recently been available in the Philippines. It involves a radiopharmaceutical with high-affinity binding to amyloid plaques which for a time were thought to be central pathological finding for Alzheimer dementia. This study describes the first four amyloid PET scans in the Philippines and detail the protocol as well as interpretation of such studies. The procedure is not as simple and reproducible as one might think hence following the recommended protocol and interpretation guidelines are of utmost importance. We recommend standardization of the reporting of results for all centers that will cater to patients being worked up for dementia, which include reporting SUVRs for both whole cerebellum and cerebellar cortex. More studies are recommended to generate a local Florbetaben SUVR cutoff.

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***Keywords**: amyloid PET, Alzheimer disease, diagnostic imaging, F-18 Florbetaben*

INTRODUCTION

Alzheimer's Disease

Alzheimer's disease (AD) is the most common cause of dementia accounting for two-thirds of cases. The World Alzheimer Report 2015 has estimated that 46.8 million people worldwide are living with dementia [1]. Dominguez et al. has projected the Philippines to have a total of 1,474,588 dementia cases in 2030, 1,972,067 in 2040 and 2,529,436 in 2050 with incidence at 16 per 1,000 person-year [2]. AD is a disease of the elderly, most commonly presenting at the age of 65, which presents insidiously with progressive decline. It is characterized by an accumulation of abnormal neuritic plaques and neurofibrillary tangles. Definitive diagnosis of AD requires histopathologic evidence of plaques and tangles demonstrated by Alois Alzheimer himself. The widely adapted clinical criteria used is by the National Institute on Aging and the Alzheimer's Association (NIA-AA) updated in 2011 and the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria revised in 2013. However, diagnosis is still confounded by atypical presentations such as early age and rapid decline thus the need to combine clinical features with imaging and cerebrospinal fluid (CSF) biomarkers. The National Institute on Aging-Alzheimer's Association (NIA-AA) workgroups also set criteria to help differentiate neurocognitive (NCD) subtypes using two classes of biomarkers to help diagnose AD, namely biomarkers for brain amyloid Aβ protein deposition detection and the biomarkers for downstream neuronal injury identification [3]. Evidence of amyloid deposition is based on reduced cerebrospinal fluid (CSF) Aβ42 levels and positive PET amyloid imaging, whereas the latter includes three major biomarkers, namely elevated CSF tau, reduced fluorine-18 fluorodeoxyglucose (F-18 FDG) uptake on PET in the temporoparietal lobes, and disproportionate atrophy at the medial, basal, and lateral temporal lobes on structural MRI scans. There is also a proposed staging of preclinical AD which involves objective evidence of amyloidosis with and without neurodegeneration and subtle cognitive decline.

Anatomical imaging modalities show cortical atrophy from neuronal degeneration and eventual cell loss. Different patterns of loss are associated with disease. Many, if not most, clinicians would request for the widely available MRI to support diagnosis of AD as well as to exclude other organic pathologies that can cause cognitive impairment. MRI findings of AD include widening of ventricles, parietal sulcal widening and atrophy of the posterior cingulate gyrus and precuneus, hippocampus and parahippocampal gyrus [4]. Several

scoring systems have been used as guides to assess NCD such as medial temporal lobe atrophy score, posterior cortical score and global cortical atrophy scale. The GCA scale evaluates 13 brain regions and may be confounded by age. Medial temporal atrophy is associated with mild cognitive impairment (MCI) and AD and the medial temporal lobe atrophy (MTA) score is less affected by normal aging. Posterior cortical atropy on the other hand is associated with early-onset AD and is helpful for the evaluation of atypical AD.

Positron Emission Tomography (PET)

PET becomes a marker of neuronal injury as damaged brain cells exhibit decreased uptake of F-18 FDG [5,6] and as a marker of amyloid plaque deposition when the cortex demonstrates increased uptake of the amyloid tracers. F18-FDG brain PET shows hypometabolism even before overt atrophy occurs, reflecting not only loss of cells but impaired synaptic transmission. Patterns of disease-specific decreased tracer uptake allowed F-18 FDG PET to be assist in the diagnosis of different NCDs and as prognosticating factor to predict which patients who have MCI can progress to Alzheimer dementia with reported 75-100% accuracy [7]. Advances in brain PET imaging include development of radiotracers that bind to amyloid plaques themselves. The first one to be developed is C11- Pittsburgh compound B followed by Fluorine18-based tracers like Florbetaben, Flutemetamol and Florbetapir. C11- Pittsburgh compound B use is limited to facilities who have cyclotron on-site owing to its short 20-minute half-life. Subsequent US FDA-approved F-18 radiopharmaceuticals are now preferentially used because of their longer 109.8 minute half-life. These amyloid tracers bind non-specifically to white matter and have no uptake in normal gray matter. Amyloid brain PET scans are semi-quantified into positive and negative. Negative scans demonstrate binding only the cerebral white matter while a positive scan shows uptake in both gray and white matter and hence shows loss of contrast between the two. Amyloid deposition starts even before the onset of cognitive impairment and can be seen in both AD patients and elderly patients with normal cognition hence its strength lies in its high negative predictive value, with a negative scan giving a very low likelihood of AD.

The Amyloid Imaging Task Force (AIT) was developed by the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and Alzheimer's Association to determine the Appropriate Use Criteria (AUC) of amyloid brain PET imaging [8]. The AUC will assist clinicians to determine the potential value doing an amyloid PET scan can add. It is still important to emphasize that a positive scan is not tantamount to a clinical diagnosis of Alzheimer's and that it is the ultimate clinical judgment of the clinician to decide on the diagnosis. The AIT established the following as the preamble, or the common characteristics, for patients whom AUC may be applied: presence of cognitive impairment, possibility of AD as a diagnosis and evidence of the amyloid positivity to increase diagnostic certainty, ideally sufficient to shift the management. Three appropriate indications were concluded which include 1) patients with progressive and persistent unexplained mild cognitive impairment 2) patients with possible AD (atypical course and with concomitant organic disease) and 3) progressive dementia and atypical age of onset. For the first indication, an amyloid-negative scan on the background of MCI will lead towards investigation of other causes of impairment such as vascular or traumatic. Also, combining amyloid positivity with unexplained MCI will increase the level of certainty that early AD is the cause and that it should subsequently follow that a change in management is warranted. For the second indication, it is mainly to exclude patients with typical AD and to further investigate patients already diagnosed with dementia presenting atypically or if the course is difficult to assess and those with other concomitant pathology. Lastly, amyloid PET scan may be used for patients who are young but already presenting with dementia to help plan an early course of management. Amyloid PET scan has been recommended against patients who satisfy the core-clinical criteria of AD, to determine dementia severity, to diagnose disease in those with genetic predisposition as well as determine genetic mutations, those who have cognitive complaints not confirmed clinically, asymptomatic patients and those for non-medical purposes.

Imaging Acquisition and Interpretation from SNMMI

Based on the SNMMI recommendations, physicians who interpret amyloid PET scans should have specialized in Nuclear Medicine and completed appropriate training programs from the manufacturer. Likewise, amyloid PET scans should be performed by qualified Nuclear Medicine Technologists certified by the appropriate board.

The study requisition should include 1) appropriate clinical information about the patient to justify the study

and to allow appropriate exam/study coding; 2) information about the ability of the patient to cooperate for the test is helpful; and 3) information about current medications in case mild sedation is necessary. It is also helpful to know if the patient needs to be accompanied by a guardian.

Protocol/Image acquisition

1. Before scanning, the patient should empty their bladder for maximum comfort during the study.
2. The patient should be supine with suitable head support. The entire brain should be in the field of view, including the entire cerebellum. Avoid extreme neck extension or flexion if possible. To reduce the potential for head movement, the patient should be as comfortable as possible with the head secured as completely as possible. Tape or other flexible head restraints may be employed and are often helpful.
3. ^{18}F-florbetapir, ^{18}F-flutemetamol and ^{18}F-florbetaben should be injected as a single intravenous slow-bolus in a total volume of 10 ml or less. The dose/catheter should be flushed with at least 5-15 ml 0.9% sterile sodium chloride to ensure full delivery of the dose.
4. The recommended dose/activity, waiting period, and image acquisition duration are summarized in Table 1.
5. Image acquisition should be performed in 3D data acquisition mode with appropriate data corrections.
6. Image reconstruction should include attenuation correction with typical transaxial pixel sizes between 2-3 mm and slice thickness between 2-4 mm.
7. Advise the patient to hydrate and void after the scanning session to diminish radiation exposure.

Amyloid PET imaging is interpreted both qualitatively and quantitatively. Qualitative examination by PET readers is through visual inspection of tracer deposition in the cortical gray matter of areas commonly affected in Alzheimer disease. These may be categorized into brain amyloid plaque load (BAPL) 1, 2 and 3 for no significant amyloid deposition, minor deposition, and significant deposition, respectively. BAPL 1 is amyloid-negative while BAPL 2 and 3 are positive.

OBJECTIVES

General Objective

To describe the first four Amyloid PET scans in the country, its procedure, and findings

Specific Objectives

To describe the profile of patients who underwent Amyloid PET (age, gender, indication for the scan)
To discuss the appropriate use criteria for requesting Amyloid PET

METHODS

This is a retrospective case series of four patients who underwent Amyloid brain PET scans at St Luke's Medical Center - Quezon City and Global City from July to August 2022.

Criteria for Subject Selection

Inclusion Criteria

The first four patients who completed a brain PET scan using an amyloid tracer

Exclusion Criteria

- Significant neurological disease other than early Alzheimer's disease.
- Major psychiatric disorder or symptom that can explain patient's condition
- Unstable medical conditions

Operational definitions

Brain amyloid PET scan or amyloid brain PET scan - PET scan specific for evaluating the brain using F-18 florbetaben, a radiotracer which is avid to the amyloid plaques implicated in Alzheimer's disease.

TABLE 1. Recommended Dose/Activity, waiting period and image acquisition

Radiotracer Recommended	Dose /Activity	Waiting Period	Acquisition
^{18}F-florbetapir	370 MBq (10 mCi)	30-50 minutes	10 minutes
^{18}F-flutemetamol	185 MBq (5 mCi)	90 minutes	10-20 minutes
^{18}F-florbetaben	300 MBq (8 mCi)	45-130 minutes	20 minutes

Positron emission tomography scan (PET) scan - a nuclear medicine imaging procedure using a positron-emitting nuclide to image desired parts of the body. Tracers used are dependent on the lesion being evaluated

Standardized uptake value (SUV) – a semiquantitative measurement of radiopharmaceutical uptake of a region of interest normalized to dose/radioactivity administered and volume of distribution in the body (weight or lean body mass).

SUV maximum (SUVmax) – highest SUV value in a given lesion or region of interest.

SUV mean (or mean SUV)– average SUV counts in the whole region of interest.

SUV ratio (SUVR or SUVratio) – for brain amyloid PET scans, this is the ratio of the mean SUV of the region of interest divided by the mean SUV of the reference brain region.

Description of Study Procedure

The researchers will review the database, scans, and results of the four patients who underwent Amyloid PET scans at St. Luke's Medical Center. The information will include:

- Age
- Sex
- Neurologic manifestations reported at the time of the scan
- Comorbidities
- Other imaging modalities
- Prior treatment done if any

Sample Size Estimation

No sample size was computed because only the first two patients from each branch of the hospital are included.

Data Analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the patients.

Radiopharmaceutical

Neuraceq (F-18 Florbetaben) is the locally available radiotracer for amyloid. It comes in a clear vial of 300 MBq/mL colorless solution. Similar to Fluorine-18 - based radiotracers, it decays with a half-life of approximately 110 minutes by emitting a positron radiation of 634 keV, followed by photonic annihilation radiation of 511 keV. The solution contains 30 mg sodium and 15vol% of ethanol.

The manufacturer recommends use with no dose adjustment based on age and weight. Other precautions are similar to the other radiopharmaceuticals. The medication is administered slowly via intravenous route followed by flushing using normal saline solution. For our institution, the F18-Florbetaben radiopharmaceutical is delivered by a third-party supplier.

Amyloid PET scan protocol

The following protocol is derived from the Amyloid Brain PET/CT protocol of St. Luke's Medical Center - Global City and Quezon City

- Verify patient identification (Name and date of birth at the very least)
- Verify doctor's request: (PET tracer properly indicated , with or without diagnostic CT)
- Bring patient to PET lounge and measure height and weight
- Take patient's clinical history
- Explain procedure, possible side effects and radiation precautions
- Secure consent for the procedure
- Insert IV line (or secure permission for central line access)
- Preparation of dose (re-check label of vial delivered)
- Dispense 8mCi (300 MBq) into a syringe and place in a lead-shielded container
- Recheck patency of IV line and administer radiopharmaceutical to the patient via slow IV push followed by a 10mL- saline flush
- Measure post-injection activity from the syringe and record time of administration
- Ask patient to void prior to scanning
- Perform PET scan, with or without diagnostic CT and with or without sedation, 90 minutes after tracer administration
- Strap and secure the patient to the scanning table and provide adequate head support to minimize patient motion
- Adjusts the height of the scanner table to its isocenter at 185.
- Starts the Dual CT surview (AP and Lateral Views). When the CT surview is complete, the surview image displays with a plan series box.

- Move and adjust the plan scan box for PET acquisition from base of the skull to about 1 inch above the tip of the cranium. The scan plan box for Low-dose CT will automatically adjust to the same region of interest as that of PET acquisition.
- Perform the scan of 1 bed with 20 minutes acquisition
- Nuclear Medicine physician checks scan
- Escort the patient back to the lounge and patient is sent home

PET Amyloid Interpretation

Once acquired, emission PET images and low-dose CT are sent to workstations for interpretation. Both branches of the hospitals use Biograph Vision PET/CT scanner and syngo.via workstations (Siemens Healthineers) for interpreting amyloid PET scans. These scans are read using the MM Neurology software by Siemens. The software is capable of processing images acquired using the three F-18 - based tracers against the CT attenuation correction map generated prior to the PET emission images. Non-attenuation correction images may also be used. Other imaging modalities the patients had prior were not used for correction. Options also for normalizing images using cerebellar and whole brain images are available as well. Once the images are processed, nuclear medicine physicians may view them in the axial, sagittal and coronal slices together with maximum-intensity projections. Software-generated ROIs for the cerebral and cerebellar lobes, anterior and posterior cingulate gyri, basal ganglia, and ventricles are also provided but ultimately determined by the reader. Physicians then proceed to determine F-18 Florbetaben localization. The readers compare the cortical gray matter signal intensity to the maximum white matter signal intensity. The images should be viewed in a systematic manner starting at the level of cerebellum and scrolling up through the lateral temporal and frontal lobes, then to the area of the posterior cingulate cortex and precuneus, and finally to the parietal lobe.

The manufacturers recommend scoring each reference brain region (lateral temporal lobes, frontal and parietal lobes, and precuneus/posterior cingulate gyri) as to no tracer uptake (1), moderate trader uptake (2) and pronounced tracer uptake (3), known as the regional cortical tracer uptake (RCTU) score. Brain amyloid plaque load (BAPL) scores are subsequently derived from the RCTU. BAPL 1 corresponds to having an RCTU score of 1 in each of the four brain regions (lateral temporal lobes, frontal lobes, posterior cingulate/precuneus, parietal lobes), while BAPL 2 corresponds to RCTU 2 in any or all of the four brain regions and no score of 3 in any. BAPL 3 is an RCTU score of 3 at least in one of four brain regions. BAPL 1 is the amyloid-negative scan while BAPL scores 2 and 3 are considered positive scans.

SUVRs are then computed manually by comparing the uptake values of the cortical ROI versus the cerebellar cortex with or without the whole cerebellum.

Results

Three of the four patients were elderly and one of which was in the late middle-age. Three were male. Two of the patients had stable comorbidities.

Mean radioactivity at the time of injection was 294.7 MBq of F-18 Florbetaben. Imaging was performed using a Siemens Biograph Vision 64 slice PET/CT scanner and acquired with a mean time of 90.7 minutes post tracer injection.

No reported adverse reactions to the radiotracer were noted in the four patients.

Case 1

The first patient is a 73-year-old female, hypertensive, dyslipidemic and presents with cognitive impairment. She has memory loss of recent events and with immediate recall (inability to recall details of instructions, repetitive), fears getting lost, needs assistance with maintenance medications, has word finding difficulty, not oriented to time but oriented to place, unable to construct simple geometric figures and clock drawing test. Patient is able to perform some activities of daily living and needs assistance in some. She has already been diagnosed clinically as a case of Alzheimer dementia and was previously treated with acetylcholinesterase inhibitors. Patient underwent PET amyloid imaging as a volunteer case for St. Luke's Quezon City.

Brain MRI done one year prior showed mild atrophy in the frontal, temporal and parietal lobes with mild atrophy of the choroid fissure while cognitive testing atrophy of the choroid fissure while cognitive testing reported mild Alzheimer dementia. At the time of the scan, the patient's symptoms were essentially stable.

Patient underwent the PET scan at 93 minutes post tracer injection and because of patient movement, nuclear medicine physicians decided on a delayed scan 123 minutes post tracer injection. Results showed loss of gray-white matter differentiation in the frontal lobes, parietal lobes, posterior cingulate gyrus, and lateral temporal lobes. Brain amyloid plaque load (BAPL) evaluation shows moderate beta-amyloid deposition in the aforementioned regions. SUVRs were all above the 1.478 cut-off set by Sabri et al. in 2015 including the anterior cingulate gyrus and occipital lobes [9]. The observed increase in the SUVrs during the subsequent scan however did not provide additional information other than quality control since all mean SUVs of reference regions have declined.

Quantitative analysis using the standard uptake value ratios (SUVR) normalized to the cerebellar cortex are as shown in Table 2.

Case 2

The second patient is a 56-year-old female who presented with short-term memory loss at 54 years old and family history of Alzheimer's disease. She was started on an acetylcholinesterase inhibitor one month prior to the brain PET scan. She had hysterectomy and unilateral ovarian surgery for benign findings and had no other comorbidities. A PET Amyloid scan was requested to increase diagnostic probability of early onset dementia.

Visually, there is loss of gray-white matter differentiation in the anterior and posterior cingulate gyri, frontal, parietal, occipital, and temporal lobes with corresponding elevated SUVRs as shown in Figure 2 and Table 3.

Case 3

The third patient is an 82-year-old female who complains of delayed recall and derangement in fluency. Prior brain MRI in October 2018 reported a chronic infarct in the left frontal region without any residuals. However no recent imaging modality was acquired. Patient had no prior treatment. Patient has no known comorbidities.

PET amyloid imaging acquired 90 minutes after tracer injection showed Florbetaben distribution in the white matter of the cerebrum and cerebellar peduncles. No undue florbetaben uptake is seen in the cerebral cortical gray matter. There is no loss of florbetaben gray/white matter contrast. SUVRs normalized to the cerebellar cortex were below 1.478 (see Figure 3 and Table 4).

Diagnostic CT done together with the PET scan showed no evidence of acute territorial infarct, intracranial hemorrhage or focal mass lesion with probable chronic small vessel ischemic changes, gliosis, and/or demyelination. There was mild symmetric widening of the cerebral cortical sulci on both sides, both Sylvian fissures and basal cisterns as well as the cerebellar interfolial spaces relating to volume loss. The ventricles are normal in size and configuration.

Case 4

The fourth patient is a 74-year-old male presenting with recent and distant memory loss. Recent brain MRI reported cerebral atrophy that was not uncommon for patient's age. She has no known comorbidities and no prior treatment.

PET scan acquired 90 minutes post tracer injection showed good contrast between white and gray matter in all the reference regions (see Figure 4 and Table 5).

Discussion

The AIT aimed to address several questions with regards to the application of the amyloid PET scan namely proof of technical efficacy, diagnostic accuracy, and clinical utility.

Proof of technical efficacy includes reproducibility of specific amyloid PET acquisition procedures and protocols under standardized conditions and must be applicable to the range of PET instrumentation in use.

Tracer preparation, including quality control from the third-party supplier is monitored by the manufacturer of the tracer itself. As needed site visits are conducted should concerns arise from generating the tracer. St. Luke's Medical Center makes use of the protocol as recommended in the 2016 Society of Nuclear Medicine and Molecular Imaging Procedure Standard – European Association of Nuclear Medicine Practice Guideline for Amyloid PET Imaging of the Brain. Prior to conducting

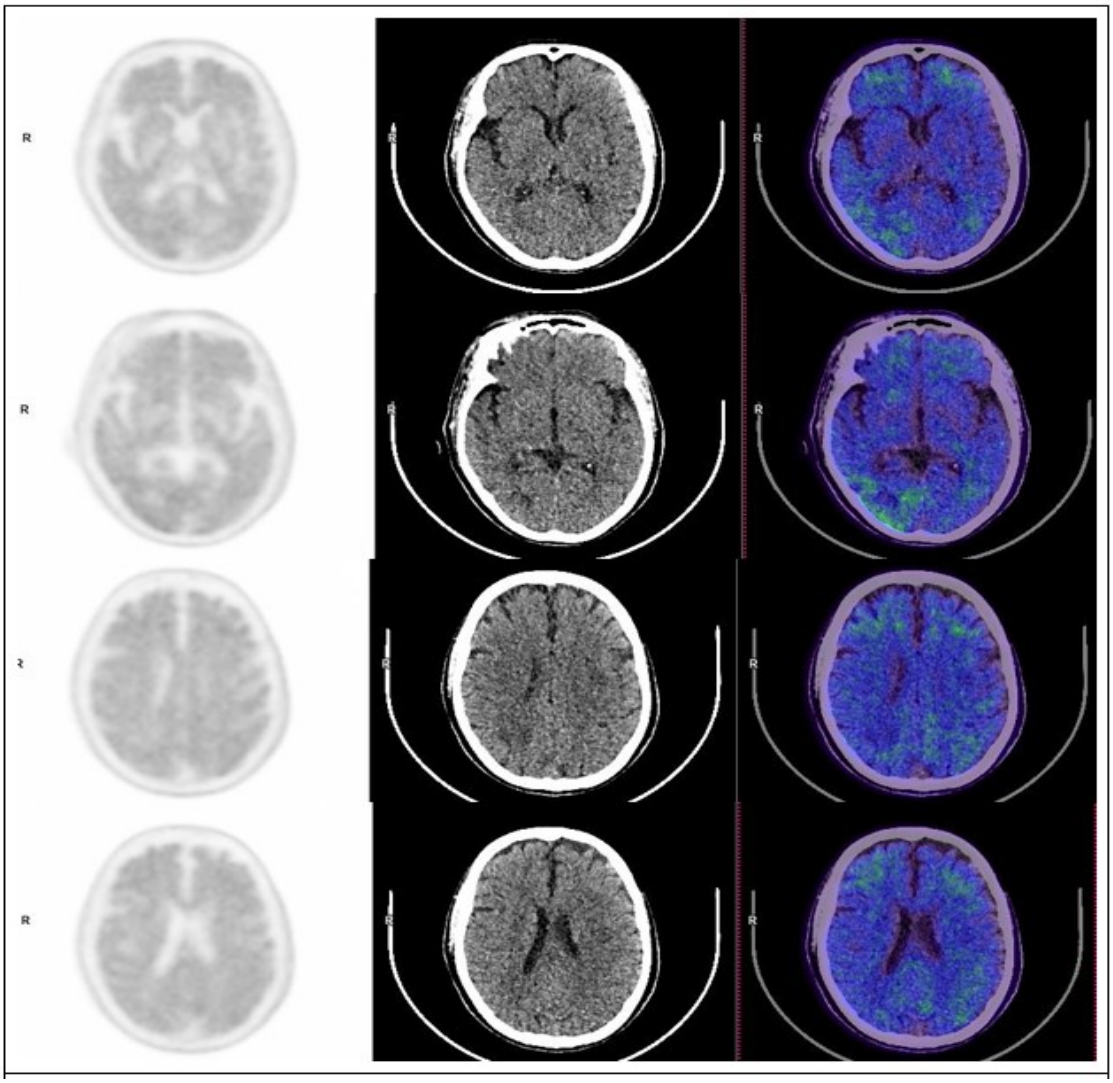

FIGURE 1. Case 1 - A Positive PET Amyloid scan

TABLE 2. Quantitative analysis using the standard uptake value ratios (SUVR) normalized to the cerebellar cortex

Regions of Interest (ROI)	Standard 90 minutes		Delayed scan	
	Mean SUV	SUVR normalized to the cerebellar cortex	Mean SUV	SUVR normalized to the cerebellar cortex
Anterior cingulate gyrus	1.54	1.64	1.39	1.65
Cerebellar cortex	0.94	-	0.84	-
Frontal lobe	1.77	1.88	1.61	1.92
Occipital lobe	2.05	2.18	1.89	2.25
Parietal lobe	1.97	2.1	1.78	2.12
Posterior cingulate gyrus	2.11	2.24	1.86	2.21
Temporal lobe	1.7	1.81	1.55	1.85

**An SUVR abnormality cut-off of 1.478 in a global cortical composite region relative to the cerebellar cortex was developed using histopathological confirmation as the standard of truth providing sensitivity (89.4%) and specificity (92.3%) to detect established Aβ pathology [9].*

**Mean SUVs were acquired using auto-generated ROIs by molecular imaging neurology software provided by the PET manufacturer.*

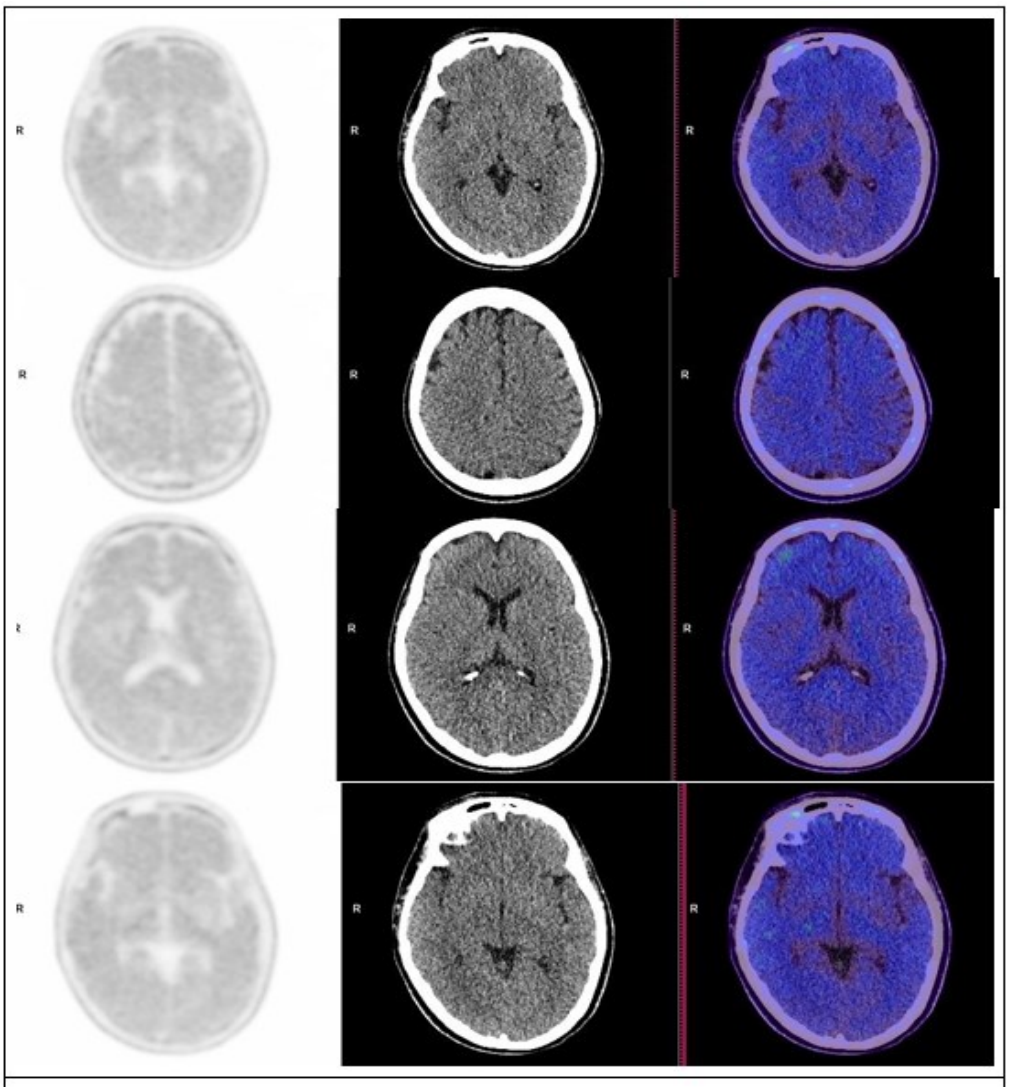

FIGURE 2. Case 2 - A Positive PET Amyloid scan

TABLE 3. Quantitative analysis using the standard uptake value ratios (SUVR) normalized to the cerebellar cortex

Regions of Interest (ROI)	Mean SUV	SUVR normalized to the cerebellar cortex**	SUVR normalized to the whole cerebellum***
Anterior cingulate gyrus	1.79	1.95	1.58
Frontal lobe	1.71	1.86	1.51
Occipital lobe	1.56	1.70	1.38
Parietal lobe	1.79	1.95	1.58
Posterior cingulate gyrus	1.86	2.02	1.65
Temporal lobe	1.72	1.87	1.52
Cerebellar cortex	0.92	-	-
Whole cerebellum	1.13	-	-

**Mean SUVs were acquired using auto-generated ROIs by molecular imaging neurology software provided by the PET manufacturer.*

***An SUVR abnormality cut-off of 1.478 in a global cortical composite region relative to the cerebellar cortex was developed using histopathological confirmation as the standard of truth providing sensitivity (89.4%) and specificity (92.3%) to detect established Aβ pathology [9].*

****Optimal SUVR cut-off for cerebellar gray matter is 1.43 and for whole cerebellum is 0.96 [10].*

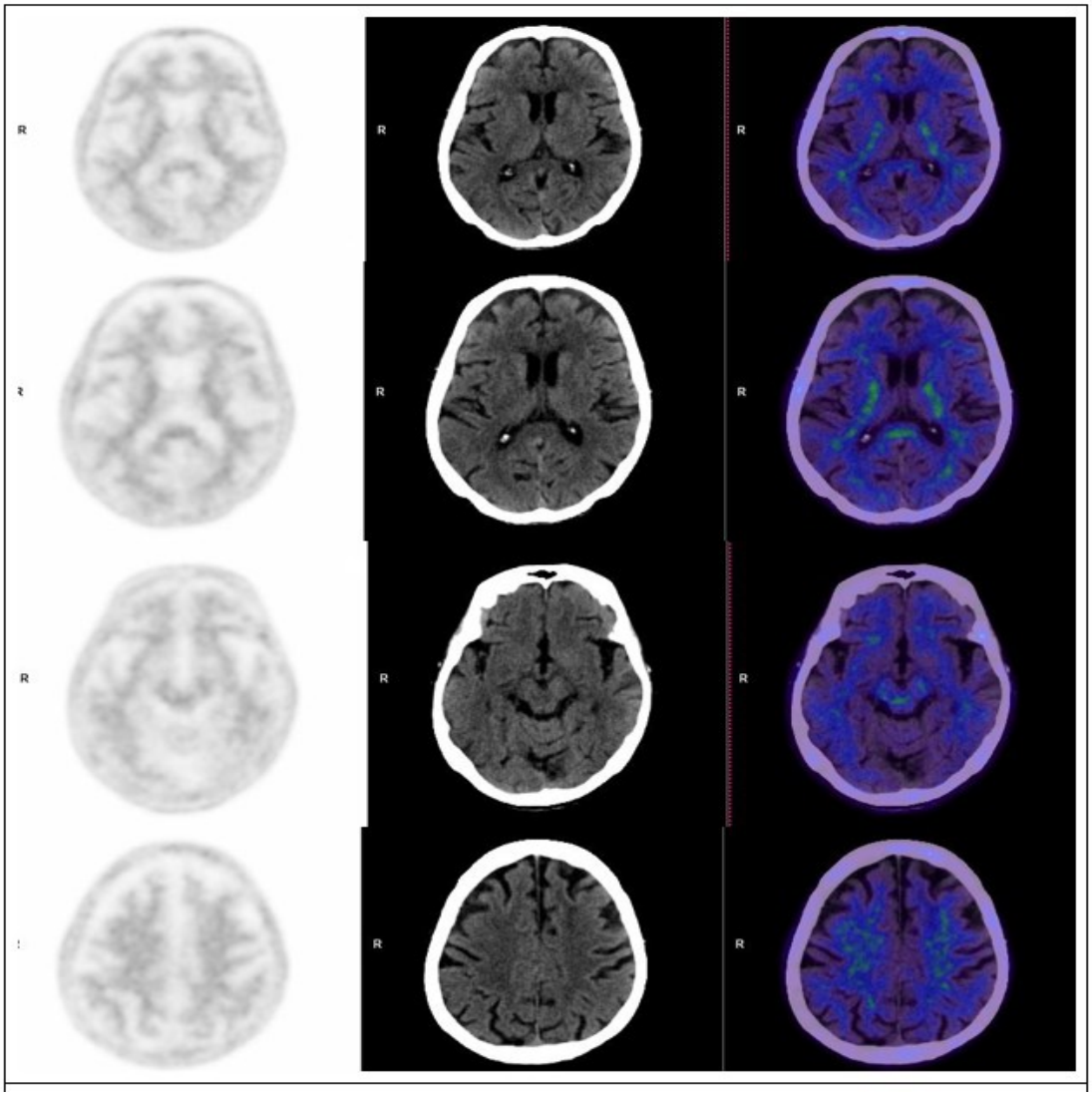

FIGURE 3. Case 3 - A Negative PET Amyloid scan showing non-specific Florbetaben uptake

TABLE 4. Quantitative analysis using the standard uptake value ratios (SUVR) normalized to the cerebellar cortex

Regions of Interest (ROI)	Mean SUV	SUVR normalized to the cerebellar cortex
Anterior cingulate gyrus	0.83	0.81
Cerebellar cortex	1.02	--
Frontal lobe	1.11	1.09
Occipital lobe	1.31	1.28
Parietal lobe	1.12	1.10
Posterior cingulate gyrus	1.30	1.27
Temporal lobe	1.20	1.18

**SUVR – standard uptake value ratio*

**An SUVR abnormality cut-off of 1.478 in a global cortical composite region relative to the cerebellar cortex was developed using histopathological confirmation as the standard of truth providing sensitivity (89.4%) and specificity (92.3%) to detect established Aβ pathology [9].*

**Mean SUVs were acquired using auto-generated ROIs by molecular imaging neurology software provided by the PET manufacturer.*

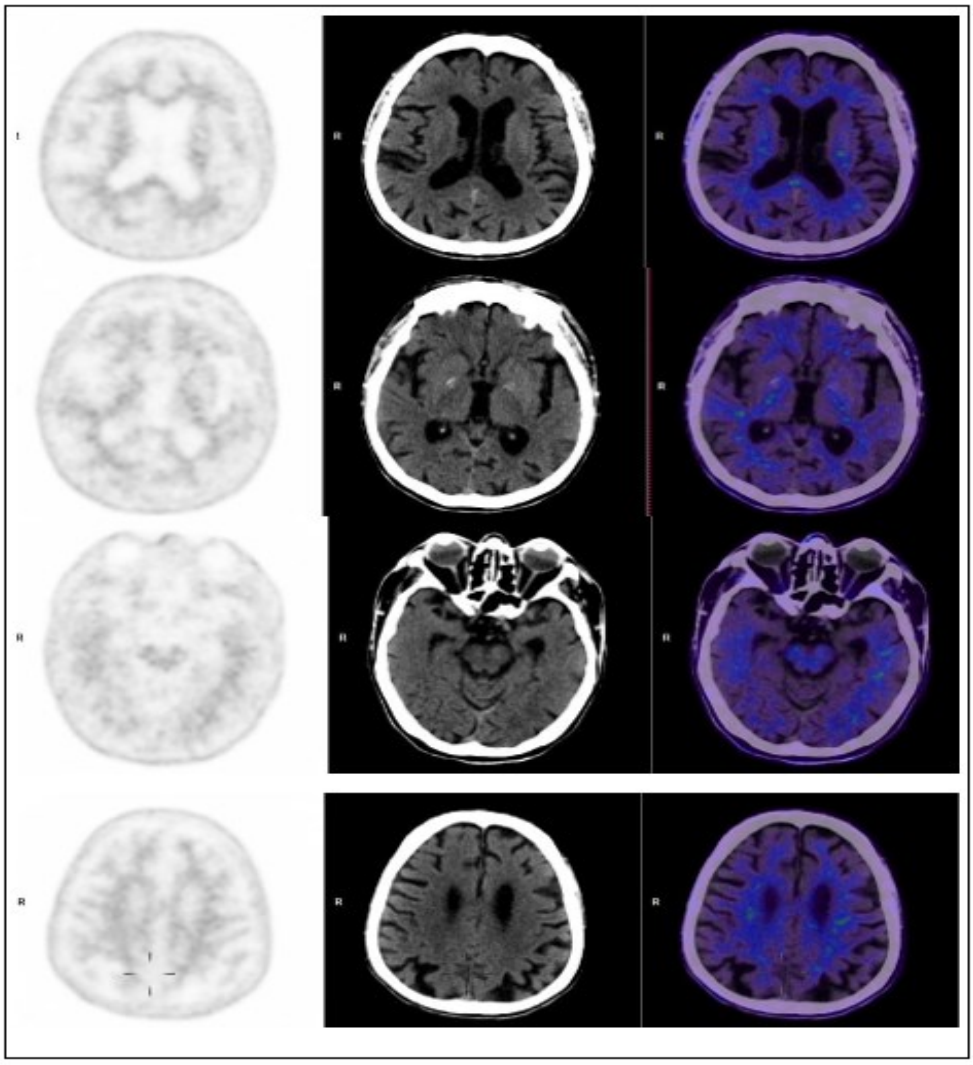

FIGURE 4. Case 4 - Negative for significant amyloid beta deposition

TABLE 5. Quantitative analysis using the standard uptake value ratios (SUVR) normalized to the cerebellar cortex

Regions of Interest (ROI)	Mean SUV	SUVR normalized to the cerebellar cortex	SUVR normalized to whole cerebellum
Anterior cingulate gyrus	0.73	1.04	0.73
Frontal lobe	0.87	1.24	0.87
Occipital lobe	0.98	1.4	0.98
Parietal lobe	0.88	1.26	0.88
Posterior cingulate gyrus	1.40	2.0	1.4
Temporal lobe	0.92	1.31	0.92
Cerebellar cortex	0.70	-	-
Whole cerebellum	1.00	-	-

**SUVR – standard uptake value ratio*

**An SUVR abnormality cut-off of 1.478 in a global cortical composite region relative to the cerebellar cortex was developed using histopathological confirmation as the standard of truth providing sensitivity (89.4%) and specificity (92.3%) to detect established Aß pathology [9].*

**Mean SUVs were acquired using auto-generated ROIs by molecular imaging neurology software provided by the PET manufacturer.*

the first amyloid PET scan in the country, the staff were given lectures to orient them with regards to the new tracer, its properties, and its indications.

The latest PET/CT scanner of both hospitals is the Siemens Biograph Vision 64 PET/CT scanner, already equipped with the necessary software application to process images acquired from the brain amyloid PET scan. The program is capable of processing the three F-18 amyloid tracers: F-18 florbetapir, florbetaben and flutemetamol despite having only F-18 florbetaben available for use in the country. The program itself is capable of generating automated regions of interest (ROIs) for the relevant regions in the brain where amyloid deposition is expected and provides standard uptake values (SUVs) and SUVRs.

Both institutions were able to administer uniform and correct radioactivity of the PET Amyloid tracer. Both were also able to image patients within the recommended 90 to 110 minute-uptake time and 20-minute acquisition time.

The AIT also recommends standardized interpretation protocols for interrater agreements. This must be set by the local professional certifying board. However, since these are the first four scans in the country, no preexisting data is available to set guidelines locally. Similar to other nuclear medicine procedures in the Philippines, protocols and references are derived from large, foreign organizations like the US FDA, SNMMI and EANM.

Diagnostic accuracy (clinical validity) of Florbetaben has been established by several studies [6, 10, 11, 12, 13]. The first amyloid tracer, C-11 Pittsburgh compound B has been the most extensively studied with proven good correlation with histopathological evidence of amyloid deposition. The F-18 based tracers flutemetamol and florbetapir have undergone tissue correlation and all three radiopharmaceuticals have been compared with C-11 PiB with good concordance [10, 11, 12,13]. F-18 Florbetaben is the first amyloid tracer studied in humans. Florbetaben's capability to increase probability of AD diagnosis has been supported by studies showing that it has high binding affinity to beta-amyloid plaques, concordant with thioflavin binding. It is not avid to α-synuclein in Lewy bodies or to tau lesions in postmortem cortices from dementia with Lewy bodies, Alzheimer's or FTLD patients. Several researches showed high Florbetaben uptake in the cortices of AD patients compared to patients with mild cognitive impairment and normal controls.

As with other elements of validation, each tracer and its associated interpretation protocol must be assessed separately. Since this is the first report of PET Amyloid Imaging in the Philippines, interpretation protocol has not yet been standardized. Clinical utility specific for Filipinos has also not been established locally.

Patients 1 and 2 had scans with visualized amyloid localization in the gray matter and with SUVRs higher than the 1.478 cut-off. Patient 1's amyloid PET scan reaffirmed the already known diagnosis of Alzheimer disease and objectively justified continuation of treatment. For Patient 2, the referring physician has started the patient on treatment for Alzheimer disease but wanted to increase the certainty of the clinical diagnosis. For the third and fourth patients, despite their advanced age, no significant amyloid deposition was noted. The negative brain amyloid PET scans discourage against dementia with amyloid deposition.patients who have histopathologically-proven amyloid

The 1.478 cut-off is derived from the study of Sabri et al. in 2015, a multicenter phase trial which used the similar PET scoring system recommended by the Neuraceq manufacturer [9]. It involved 218 patients (139 patients with AD, 5 with Dementia with Lewy bodies (DLB), 31 with other dementia disorders, 32 with non-dementia disorders and 11 who are cognitively normal). 74 of these patients had already died and whose brains became the autopsy — truth standard. Out of the 47 deposition, 44 of which had clinically-diagnosed AD. 46 out of 47 patients were read as PET amyloid positive scan. The three remaining positive scans were a case of DLB, one had another dementia disorder and one is not clinically diagnosed with dementia. This resulted in a sensitivity of 97.9% (95% CI 93.8-100%) and a specificity of 88.9% (95% CI 77.0–100%) for florbetaben PET imaging detection of amyloid plaques. Other studies have advocated an SUVR of 1.23 to 1.45.

Despite several studies suggesting using SUVRs, a study by Bullich et al. in 2016 involving 78 autopsied patients whose SUVRs were calculated from whole cerebellum and cerebellar cortical gray matter recommended that we prefer the use of visual assessment and limit the contribution of SUVRs in the interpretation of PET amyloid scans [13]. Subsequent research of two of the authors of this article stated that SUVRs were developed mainly to discriminate patients with amyloid-beta pathology from those who are cognitively normal hence they cannot be used to detect earliest amyloid deposition [10]. They however support SUVRs to increase the accuracy of non-expert readers who may

benefit from the additional contribution.

The procedure of PET Amyloid imaging is uniform for all of the four scans. One scan did not report SUVRs normalized to the whole cerebellum and one scan had delayed imaging due to patient motion. All four scans used visual assessment and SUVR quantification using the 1.478 cut-off.

RECOMMENDATIONS

For future PET Amyloid imaging as it is relatively new, the researchers would like to firstly highlight the importance of the appropriate use criteria set by AIT. The procedure is costly for the average Filipino, hence prudence should be exercised when requesting the test. Clinicians must weigh the pre-test and post-test probability and the expected benefit to their patient.

Second, institutions should always abide by the imaging guidelines to establish uniformity of the procedure. Interpretation confounders can arise starting from tracer administration up to interpretation.

We also recommend the reporting of SUVR cut-offs but primarily for future research purposes. To date, available studies regarding SUVR cut-offs employ them to support the findings of visual assessment which is the currently accepted method, and as a means of a semi-quantitative measurement. Calculating SUVRs based on both whole cerebellum and cerebellar cortex is also suggested until a local SUVR cut-off is established and validated.

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