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Management Impact of Imaging Brain Vesicular Monoamine Transporter type-2 (VMAT2) in Clinically Uncertain Parkinsonian Syndrome (CUPS) with ^{18}F-AV133 and PET.

Paschal K Alexander[1], Yenni Lie[1], Gareth Jones[1], Chomalaven Sivaratnam[1], Svetlana Bozinvski[1], Rachel S. Mulligan[1], Kenneth Young[1], Victor L. Villemagne[1, 2,3], Christopher C. Rowe[1,2,3].

[1.] Department of Molecular Imaging and Therapy, Austin Health, Melbourne, Victoria, Australia.

[2] Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, Victoria, Australia.

[3] Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia.

Corresponding author:

Paschal K Alexander, Medical Research Fellow, Department of Molecular Imaging and Therapy, Austin Health, 145 Studley Road, Heidelberg, Vic. 3084, Australia. Telephone: +61-3-9496 5663. Fax: +61-3-9496 5663. Email: Paschal. Alexander@austin.org.au

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ABSTRACT

Objectives: Idiopathic Parkinson's disease (iPD) is a common neurodegenerative disorder where misdiagnosis occurs in up to 30% of patients after initial assessment and in 10-15% even after long-term follow-up. Vesicular monoamine transporter type II (VMAT2) imaging with Positron Emission Tomography (PET) allows assessment of the integrity of the presynaptic dopaminergic pathway. We investigated the management impact of VMAT2 imaging in patients with Clinically Uncertain Parkinsonian Syndromes (CUPS).

Methods: Forty-seven patients with CUPS (56.9 +/-14.9 years, range 21-80) were referred from movement disorder specialists. All participants underwent a 20-minute PET acquisition 2 hours post injection of 250 MBq of ^{18}F-AV-133, and the resulting images were quantitatively assessed. Clinical impact was recorded as high, moderate or low based on diagnosis and management questionnaires completed by the referring specialists pre and post release of the PET results. Management impact was high if there was a change in diagnostic category; moderate if there was a change in medication and low if there was no change.

Results: VMAT2 PET changed the diagnosis in 11 (23%) and medication in 25 (53%) participants. Management impact was high in 23%, moderate in 38% and low in 39% of the participants. High

diagnostic confidence increased from 11% of patients to 80% after the release of the scan results.

Conclusions: ^{18}F-AV-133 had substantial management impact in patients with Clinically Uncertain Parkinsonian Syndromes. This suggests that VMAT2 imaging with ^{18}F-AV133 might improve diagnosis, prognosis and appropriate use of medication, translating into better patient outcomes.

Keywords: management impact; molecular imaging; Parkinson disease; PET; VMAT2

INTRODUCTION

Idiopathic Parkinson's disease is a common neurodegenerative disorder with an incidence of about 17 per 100 000 per year (*1,2*). The pathophysiology of iPD includes loss of dopaminergic neurons in the substantia nigra and thereby loss of dopaminergic terminals in the striatum. This terminal loss correlates with the extrapyramidal symptoms of the disease. While bradykinesia, rigidity and resting tremor remain the clinical diagnostic criteria for iPD, reports of diagnostic accuracy compared to post-mortem diagnosis varied from 70% in early stage disease to 90% in advanced stage in a tertiary referral movement disorder clinic (*3-5*). However, about one in five patients presenting with Parkinsonian features do not meet these diagnostic criteria (*6*) or may have additional clinical features suggesting another disease process. Under these circumstances the patient may be labelled as clinically uncertain Parkinson's syndrome (*7*). Several conditions might overlap with iPD leading to misdiagnosis or diagnostic uncertainty. Among these, disorders where the dopaminergic pathways are intact include essential tremor, dystonia, drug induced Parkinsonism, and symptoms without dopaminergic deficit, or disorders where there is dopaminergic neuronal loss plus more extensive neurodegeneration, such as multiple system atrophy, progressive supranuclear palsy and corticobasal degeneration.

The shortcomings of clinical examination alone and the advantages of early diagnosis and early treatment necessitate a method for more accurate and early diagnosis.

The integrity of the nigrostriatal system can be evaluated non-invasively using PET and single photon emission computed tomography to provide clinical information that can assist in the early and differential diagnosis of iPD (*8-14*). Several radioligands have been developed for this purpose to image either presynaptic targets such as the dopamine transporter (DAT), VMAT2, dihydroxyphenylalanine decarboxylase activity or postsynaptic D2 dopamine receptors (*6*). VMAT2 is involved in the uptake and storage of dopamine and other monoamines into presynaptic vesicles. It is mainly located at the nerve endings as well as nerve cell bodies and dendrites (*15*). Reduction in VMAT2 in the striatum reflects loss of nigrostriatal terminals (*16,17*). The in vivo measurement of VMAT2 density has been shown to be potentially very useful for the early and differential diagnosis of iPD (*18,19*).

^{18}F-AV-133 is an ^{18}F–labelled dihydrotetrabenazine analogue. This compound binds selectively and with high affinity to VMAT2 (*19,20*) and can sensitively detect monoaminergic terminal reductions in PD and DLB patients (*15*). While DAT imaging has been shown to improve diagnostic accuracy for iPD and have substantial management impact in CUPS, VMAT2 imaging with ^{18}F-AV-133 has potential advantages such

as better image quality and quantification, shorter time between tracer administration and scan, shorter scan duration and no requirement for prior blockade of the thyroid to prevent radioactive iodine uptake.

This study aims to assess the impact of VMAT2 imaging using ^{18}F-AV133, on management of clinically uncertain Parkinson's syndrome.

METHODS

Study Design and Subjects Selection

The study was approved by the Austin Health Human Research Ethics Committee. All of the participants provided written informed consent prior to their participation in the study. The study utilized a prospective experimental study design. Study participants comprised of patients with atypical features of Parkinsonism who were referred from movement disorder specialists practicing in private or public clinics across Melbourne, Australia.

Inclusion Criteria

Participants were required to be older than 18 years and English speaking. Participants were also required to have more

than seven years of education and to have adequate visual and auditory acuity to complete the clinical and cognitive assessment.

Exclusion Criteria

Patients were excluded if they had a history of cancer (other than skin or in situ prostate cancer) within the previous five years. Persons were also excluded if they were unable to give informed written consent.

Pregnancy was excluded in women of childbearing age by blood test just prior to the scan.

Assessments and Evaluation

Each participant underwent neuropsychological assessment and neurological examination. The neuropsychological assessment involved the mini-mental state examination, clinical dementia rating, hospital anxiety and depression scale, logical memory score and verbal fluency scores. The neurological evaluation comprised Hoehn and Yahr score, and a motor subscale of the Unified Parkinson Disease Rating Scale (UPDRS) score.

Questionnaires

The referring neurologists were required to complete diagnosis and management questionnaires at baseline and after the release of the AV-133 PET scan results.

The baseline questionnaire detailed the current management, the investigations completed, the most likely diagnosis from six categories – psychosomatic, dystonia, neurodegenerative, drug induced, cerebrovascular disease, other (including essential tremor), and the confidence, expressed as a percentage, in that diagnosis. If the clinician thought the diagnosis was a neurodegenerative disorder, they were required to specify whether this was thought to be Parkinson's Disease, Multiple System Atrophy, Progressive Supranuclear Palsy, Cortical Basal Ganglionic Degeneration, uncertain type or other. Their confidence in the specific neurodegenerative disorder diagnosis was also recorded.

Details of proposed long-term management, including medication plan, referral to other health providers and follow-up visit frequency, were also recorded. Subsequent questionnaires were issued after the scan results were released and the management impact determined on these same areas.

Management impact

Outcome measures were defined as high, moderate or low management impact. Management impact was defined as high if there was a change in diagnostic category from a progressive neurodegenerative disorder to a non-degenerative disorder or vice versa after the PET scan results; moderate if there was a resultant change in medication; or low if the results confirmed clinical diagnosis or the result was discrepant and ignored.

Confidence in diagnosis was rated into three categories as possible (<50%), likely (>50%) and highly likely/definite (>90%) both before and after scan release.

PET Acquisition

A 20-min emission PET scan was obtained two hours after intravenous administration of ~250 MBq of ^{18}F-AV133. The images were reconstructed using a 3D row-action maximum-likelihood algorithm (*15*) and were corrected for attenuation using a transmission scan from a rotating Caesium-137 source.

Image Analysis

As previously reported, tissue ratios for the caudate nuclei, anterior and posterior putamen were calculated using the primary visual cortex as a reference region, and compared to a locally derived normal range (*21*) (Fig. 1). A reduction of more than 50% in the most affected

posterior putamen compared to the mean of a previously obtained normal control group (Fig. 2) was considered consistent with iPD or PD plus syndrome. This cut-off was based on observations from histopathological studies that have documented loss of more than 50% of dopamine terminal markers in the posterior putamen in early symptomatic PD cases (*22*).

RESULTS

Patient Demographics

The study consisted of 47 participants. Patient demographics are displayed in table 1. There were 25 males (53%) and 22 females (47%) who ranged in age from 21 to 80 years. The mean age was 56.3 years. Only one participant had a Hoehn and Yahr score of zero and no one had a score of 4.0 or 5.0. The mean baseline MMSE score was 29 and no participant had a score below 25.

Diagnosis pre-scan

The majority of patients, 30 (64%), were initially diagnosed as having neurodegenerative disease as seen in table 2. Of these, 20 were thought to have iPD, 7 unknown, 1 multiple system atrophy, 1 progressive supranuclear palsy and 1 other. Seven (15%) patients were

thought to have a psychogenic condition; 4 (9%) were diagnosed as dystonia and 3 (6%) as drug induced. Three patients were thought to have essential tremor (classified as other).

Scan Findings

Twenty-two patients (47%) had abnormal scans (i.e. more than 50% reduction in ^{18}F-AV133 uptake in the posterior putamen). In these abnormal scans, reduction was more than 80% in 14, 60-79% in 5, and 51-59% in 2 (Fig. 2). Age correction was applied but had no impact on the measures.

Diagnosis change

Data for the diagnosis change was obtained from the management impact questionnaires. More than 75% of the post-scan release questionnaires were completed within four months of the baseline questionnaire and all were returned within a year.

The initial diagnosis was changed in 12 (26%) patients after the release of the scan result. One of these was a change from dystonia to psychogenic and so was not considered as high impact based on our definition. Of the normal scans, the diagnosis was changed in 36% (9/25) and that value was 9% (2/22) for the abnormal scans.

Medication Change

With regard to medications, 53% (25/47) of the participants had changes to their regime after the scan results were released. When the scan results were abnormal, 54.5% (12/22) had change, predominantly an increase in PD treatment, while 52% (13/25) of those with a normal scan had change, predominantly withdrawal of PD medications.

Management Impact And Diagnostic Confidence

Management impact was high in 23%, moderate in 38% and low in 39% (Fig. 3). Prior to the PET scan, clinician confidence was high (very likely/definite) for only 11% of the patients, but increased to 81% after the release of the scan results. Overall, there was an increase in diagnostic confidence in 74% of patients after the scan.

Confidence in the diagnosis increased post-scan as illustrated in table 3. This occurred whether the scan results were abnormal (16/22 or 73%) or normal (19/25 or 76%). In addition, 4 out of the 25 (16%) normal scans resulted in a decrease in confidence with or without a change in diagnosis. This was only the case for 1 of the 22 abnormal scans (4.5%).

DISCUSSION

This study sought to determine if the result of VMAT2 imaging with ^{18}F-AV133 impacted the diagnosis and clinical management of patients with CUPS. Our findings indicated a moderate to high impact in 61% of the cases (38% moderate and 23% high impact). We obtained an increase in diagnostic confidence in 74% of cases after the scan result was released and a 23% change in diagnosis.

These findings are comparable to studies using the single photon emission computed tomography, dopamine transporter-imaging agent, Iodine-123 FP-CIT (DaTscan) when assessing loss of striatal dopaminergic innervation in CUPS. Seifert et al. (2013) reported that the DaTscan result led to a change of diagnosis in 31% and impacted clinical management in 58% of their patients (*23*). This is comparable to our values of 23% diagnosis change and 61% impact (combined moderate and high). However their study was retrospective compared to our prospective design. Lokkegaerd et al. (2002) demonstrated that the results of DaTscan led to a change of either diagnosis or clinical management in 27% of patients (*24*).

Clinician confidence was also impacted by the ^{18}F-AV133 scans. Clinician confidence increased in 74% of the cases after the scan result was revealed. DaTscan studies conducted by both Kupsch et al (2012) and Seifert et al (2013) also demonstrated significant changes in

confidence in diagnosis post release of result (*23,25*). Interestingly, Kupsch et al (2012) followed up after 4 weeks, 12 weeks and 1 year and reported a further increase in confidence in the diagnosis at each follow-up interval (*25*) indicating that diagnosis assisted by striatal dopaminergic innervation imaging remained robust over time.

In our study, clinician confidence was equally increased whether the scan was normal or abnormal. This contrasts with the findings by Catafau et al. (2004) in their study with DaTscan. They found an increase in confidence when the scan results were abnormal but a decrease in confidence when the scan results were normal (*7*).

Medication regime was impacted in 53% of the patients. The changes ranged from commencement of a new agent, cessation of an agent, to change in the dose. Studies conducted with DaTscan also attribute a significant portion of their management change post-scan, to medication changes (*7,23-25*).

Of the 22 patients with abnormal scans, 14 had a reduction in VMAT2 binding compared to the mean of controls, of more than 80%. This highlights the fact that diagnostic uncertainty can manifest even with a high degree of dopaminergic loss.

We chose a reduction in relative binding in the posterior putamen of greater than 50% to be abnormal. This value was chosen as

previous post mortem studies have shown that a reduction of about 50% of dopaminergic neurons was necessary to produce clinical symptoms sufficient for the diagnosis of Parkinson's disease to be made (*22*). In our group, 50% reduction corresponds to 3 standard deviations below the mean of a reference group consisting of healthy normal adults that underwent VMAT2 PET imaging with ^{18}F-AV133. As such, we believe that we are justified in using that value for this application though it would not be appropriate if preclinical detection of iPD is the goal.

There were some limitations to this study. Firstly, there was no pathological confirmation of the diagnosis in those with abnormal scans nor was there confirmation from longitudinal clinical follow up. Prior studies have demonstrated high concordance of DaTscan findings with post mortem diagnosis and similar studies would be useful for VMAT2 imaging.

The study population was generally referred from movement disorder specialists in Melbourne and so the demographics of the study participants reflect that of the local, predominantly Caucasian population. There was no control arm in this study such as CUPS patients without VMAT2 imaging. Therefore it is possible that diagnosis and clinician confidence changed due to the passage of time or repeat clinical assessment. A controlled study is needed to address this issue.

The findings in this study provide further evidence for the use of imaging as a complementary aide in managing CUPS. While the findings are very similar to those obtained with the single photon emission computed tomography imaging agent DaTscan, ^{18}F-AV133 PET has logistic advantages including shorter uptake and scanning times and no patient preparation. It also produces high quality images that allow more accurate quantification and this may be important if monitoring change over time as in therapeutic drug trials.

CONCLUSION

Significant impact in management and confidence in the diagnosis was derived from imaging VMAT2 with ^{18}F-AV133 and PET in patients with CUPS.

FINANCIAL DISCLOSURE

This was an investigator-initiated study supported by a grant from Avid Radiopharmaceuticals. Christopher Rowe MD has received research grants from GE Healthcare, Piramal Imaging, Navidea and Avid Radiopharmaceuticals. Victor L. Villemagne MD has been an honorary speaker for Avid Radiopharmaceuticals.

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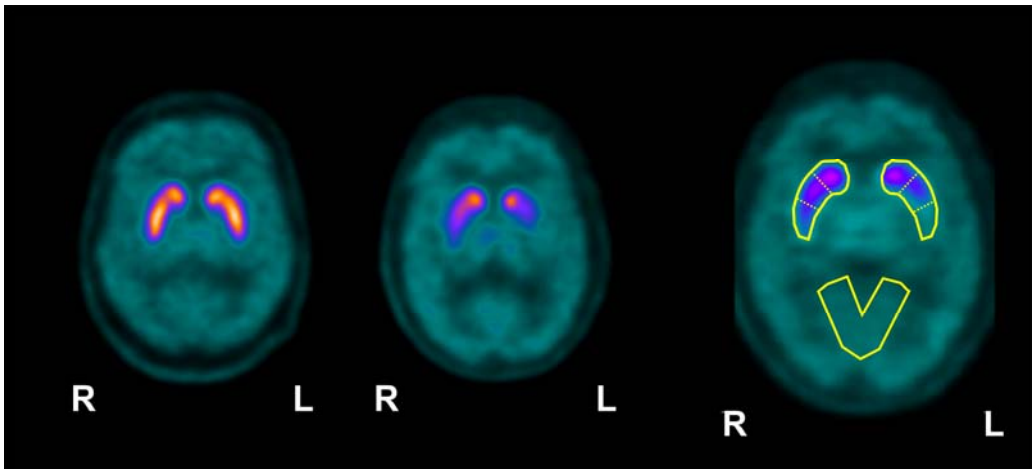
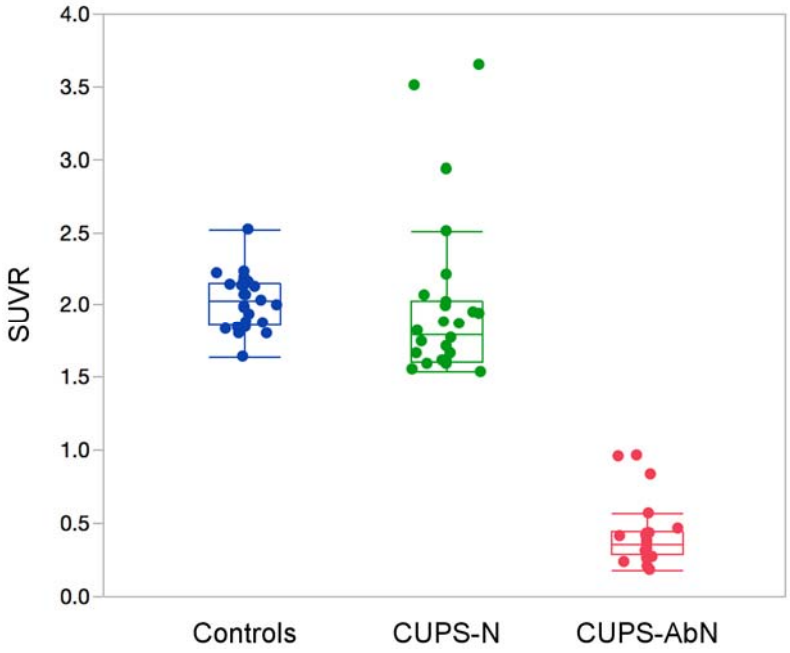
Figure 1



Representative ^{18}F-AV-133 VMAT2 PET images of a normal age-matched volunteer (A) showing symmetrical distribution of the tracer in the basal ganglia, and a Parkinson's disease patient (B) showing marked reduced and asymmetric tracer retention in the basal ganglia, more pronounced in the left putamen. Images were quantified using a predefined region of interest (ROI) template (C) that was applied on spatially normalized ^{18}F-AV-133 images. The ROI template sampled the caudate nuclei, anterior and posterior putamen as well as the primary visual cortex that was used as reference region.

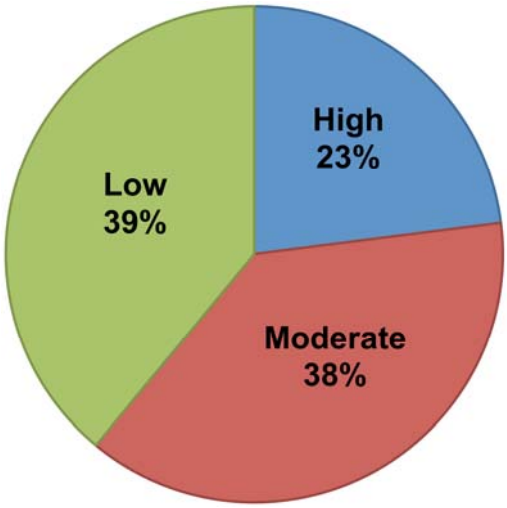
Abbreviations: L and R denotes left and right, respectively

Figure 2



Standard uptake value ratios, (SUVR's) of the Posterior Putamen in normal controls, (blue), CUPS with normal scans (CUPS-N) (green) and CUPS with abnormal scans, (CUPS-AbN) (red).

Figure 3



Post scan management impact.

Table 1 Patient demographics

Characteristics	
Age at baseline	
Mean (+/-SD)	56.9 (+/- 14.9)
Range (min, max)	21-80
Gender	
Male	25
Female	22
UPDRS score motor, mean (+/-SD)	8.4 (+/-6)
UPDRS score rigidity (+/-SD)	0.7 (+/-1.0)
UPDRS score Bradykinesia (+/- SD)	0.6 (+/- 0.7)
Hoehn & Yahr Score	
0	1
1.0 Unilateral	19
1.5 Unilateral plus axial involvement	4
2.0 Bilateral disease without balance impairment	10
2.5 mild bilateral disease with recovery on pull test	5
3.0 mild to moderate bilateral disease	6
4.0 severe disability	0
5.0 wheelchair bound or bedridden	0
MMSE score at baseline	
Mean (+/-SD)	29.1(+/- 1.4)
Range (Min, max)	25,30

Table 2 Scan results and diagnosis pre and post results

Patient Number	Scan Result	Pre-scan Diagnosis	Post-scan Diagnosis
1	Positive	Dystonia	Neurodegenerative
2	Positive	Neurodegenerative	Neurodegenerative
3	Negative	Dystonia	Psychogenic
4	Positive	Neurodegenerative	Neurodegenerative
5	Positive	Neurodegenerative	Neurodegenerative
6	Negative	Neurodegenerative	Other-benign tremor
7	Positive	Neurodegenerative	Neurodegenerative
8	Positive	Neurodegenerative	Neurodegenerative
9	Positive	Neurodegenerative	Neurodegenerative
10	Positive	Neurodegenerative	Neurodegenerative
11	Negative	Drug-induced	Drug-induced
12	Negative	Psychogenic	Psychogenic
13	Negative	Neurodegenerative	Other
14	Negative	Neurodegenerative	Other-benign tremor
15	Positive	Neurodegenerative	Neurodegenerative
16	Positive	Neurodegenerative	Neurodegenerative
17	Negative	Psychogenic	Psychogenic
18	Negative	Neurodegenerative	Psychogenic
19	Negative	Psychogenic	Psychogenic
20	Positive	Neurodegenerative	Neurodegenerative
21	Positive	Neurodegenerative	Neurodegenerative
22	Positive	Neurodegenerative	Neurodegenerative
23	Negative	Psychogenic	Psychogenic
24	Positive	Neurodegenerative	Neurodegenerative
25	Negative	Other	Other
26	Positive	Neurodegenerative	Neurodegenerative
27	Positive	Neurodegenerative	Neurodegenerative
28	Negative	Neurodegenerative	Neurodegenerative
29	Negative	Other	Other
30	Negative	Psychogenic	Psychogenic
31	Positive	Neurodegenerative	Neurodegenerative
32	Negative	Neurodegenerative	Psychogenic
33	Positive	Neurodegenerative	Neurodegenerative
34	Positive	Other	Neurodegenerative
35	Negative	Psychogenic	Psychogenic
36	Negative	Neurodegenerative	Dystonia
37	Negative	Neurodegenerative	Cerebral Vascular disease
38	Negative	Drug-induced	Drug-induced
39	Negative	Dystonia	Dystonia
40	Positive	Neurodegenerative	Neurodegenerative
41	Positive	Neurodegenerative	Neurodegenerative
42	Negative	Neurodegenerative	Drug-induced
43	Negative	Neurodegenerative	Other
44	Positive	Neurodegenerative	Neurodegenerative
45	Negative	Psychogenic	Psychogenic
46	Negative	Drug-induced	Drug-induced
47	Negative	Dystonia	Dystonia

Table 3 Clinical Confidence Pre-scan and Post-scan

	Number Pre-scan	**Number Post-scan**
Possible	15	6
Likely	27	3
Very Likely/Definite	5	38