Ioflupane 123I (DAT scan) SPECT identifies dopamine receptor dysfunction early in the disease course in progressive apraxia of speech

Article *in* Journal of Neurology · May 2020

DOI: 10.1007/s00415-020-09883-4

CITATIONS
2

READS
28

12 authors, including:

Rene Utianski
Mayo Clinic - Rochester
66 PUBLICATIONS **360** CITATIONS
SEE PROFILE

Hugo Botha
Mayo Foundation for Medical Education and Research
75 PUBLICATIONS **565** CITATIONS
SEE PROFILE

Joseph R Duffy
Mayo Foundation for Medical Education and Research
226 PUBLICATIONS **6,427** CITATIONS
SEE PROFILE

Heather Clark
Mayo Foundation for Medical Education and Research
72 PUBLICATIONS **1,393** CITATIONS
SEE PROFILE

Journal of Neurology
https://doi.org/10.1007/s00415-020-09883-4

ORIGINAL COMMUNICATION

Ioflupane 123I (DAT scan) SPECT identifies dopamine receptor dysfunction early in the disease course in progressive apraxia of speech

Zeynep Idil Seckin[1] · Jennifer L. Whitwell[2] · Rene L. Utianski[1] · Hugo Botha[1] · Farwa Ali[1] · Joseph R. Duffy[1] · Heather M. Clark[1] · Mary M. Machulda[3] · Lennon G. Jordan[2] · Hoon-Ki Min[2] · Val J. Lowe[2] · Keith A. Josephs[1]

Received: 6 January 2020 / Revised: 29 April 2020 / Accepted: 2 May 2020

Abstract

Objective To describe ^{123}I-FP-CIT (DAT scan) SPECT findings in progressive apraxia of speech (PAOS) patients and to compare those findings with progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS).

Background PAOS is a neurodegenerative syndrome in which patients present with apraxia of speech, a motor speech disorder affecting programming and planning of speech. Patients with PAOS predictably develop Parkinsonism. DAT scan is a neuroimaging tool that assesses the integrity of presynaptic dopamine transporters in striatum and is usually abnormal in PSP and CBS.

Methods As part of an NIH-funded grant, we performed a DAT scan on 17 PAOS patients early in the disease course. DaTQUANT software was used to quantify uptake in the left and right caudate and anterior/posterior putamen, with striatum to background ratios (SBRs). The PAOS cohort was compared to 15 PSP and 8 CBS patients.

Results Five PAOS patients (29%) showed abnormalities in at least one striatal region on DAT scan. When the five PAOS patients with abnormal DAT were compared to the PSP and CBS patients, the only difference observed was lower uptake in the posterior putamen in PSP ($p = 0.03$). There were no differences is putamen/caudate ratio or in symmetry of uptake, across all groups. There was also no difference in MDS-UPDRS-III scores between PAOS patients with and without abnormal DAT scans ($p = 0.56$).

Conclusions Abnormal DAT scan is observed early in the disease course in approximately 30% of PAOS patients, with striatal abnormalities similar to those in PSP and CBS.

Keywords Progressive apraxia of speech (PAOS) · Progressive supranuclear palsy (PSP) · Corticobasal syndrome (CBS) · Parkinsonism · Dopamine receptor · ^{123}I-FP-CIT (DAT scan) SPECT

Introduction

Apraxia of speech (AOS) is a motor speech disorder in which the main problem is impaired planning and/or programming of speech [1]. Apraxia of speech may arise acutely after a left hemisphere stroke or may result from neurodegeneration, starting insidiously and progressing over time [2, 3]. Patients with progressive apraxia of speech (PAOS) sometimes can have other accompanying features that often are less severe, for example, agrammatic aphasia [4]. Whenever a patient presents solely with AOS in the absence of aphasia, the syndrome is referred to as primary progressive AOS (PPAOS) [5]. We have shown that in patients with PAOS, including those with PPAOS, motor parkinsonian symptoms, including bradykinesia and rigidity often develop over time [2, 6–9]. In one of our longitudinal studies of 13 PPAOS patients followed for 2 ½ years, average of 7 years from the disease onset, 10 developed parkinsonian symptoms, with a subset developing features that overlap with progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS)

✉ Keith A. Josephs
josephs.keith@mayo.edu

[1] Department of Neurology, Mayo Clinic College of Medicine and Science, 200 1st Street S.W., Rochester, MN 55905, USA

[2] Department of Radiology, Mayo Clinic, Rochester, MN, USA

[3] Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA

Published online: 09 May 2020

within 5 years from onset [2]. In keeping with this observation is the fact that PAOS patients commonly show tau pathology, either PSP or corticobasal degeneration at death [6].

Ioflupane 123I dopamine transporter (DAT) SPECT was first approved by the FDA, in 2011, to differentiate Parkinson disease from essential tremor given that DAT scans enable the visualization of presynaptic dopamine transporter function in the striatum and hence inform on the integrity of the nigrostriatal dopaminergic system [10, 11]. Patients with parkinsonism including CBS and PSP show abnormalities on DAT scan with both CBS and PSP patients having loss of presynaptic dopamine transporter function [12–14].

Given the fact that PAOS patients commonly develop parkinsonism with clinical features that overlap with those of PSP and CBS, suggesting an involvement of the nigrostriatal dopaminergic system, we aimed to describe Ioflupane 123I DAT scan findings in PAOS, and also to compare DAT scan findings in PAOS to PSP and CBS. We hypothesized that DAT scan would be abnormal in at least some PAOS patients and show similar DAT scan abnormalities as in PSP and in CBS.

Methods

Patient recruitment and evaluation

Patients with PAOS ($n = 17$) were recruited by the Mayo Clinic, Neurodegenerative Research Group (NRG), between February 2018 and August 2019. All patients entered into an NIH-funded study and underwent a detailed speech and language, neurological and neuropsychological evaluation, and a DAT scan. DAT scan imaging was done in their first research visit. To be included in the study, all patients had to present with progressive AOS. Patients with concurrent illnesses that could account for the speech deficits, such as traumatic brain injury, stroke or developmental syndromes, and patients meeting criteria for another neurodegenerative disease, such as Alzheimer's type dementia [15], dementia with Lewy bodies [16] behavioral variant frontotemporal dementia [17], probable PSP [18], CBS [19], multiple system atrophy [20], or motor neuron disease [21] were excluded.

The speech and language evaluation included the Apraxia of Speech Rating Scale (ASRS-3 score) [22] which determines the presence and prominence of a number of clinical features associated with AOS and the Western Aphasia Battery Aphasia Quotient (WAB-AQ) [23] to assess aphasia presence and severity. Judgments concerning the presence/absence of both AOS and aphasia were made by consensus between at least two speech–language pathologists based on reviewing video recordings of the entire speech and language examination, as previously described in detail [5]. The neurological and neuropsychological testing included the PSP Rating Scale [24] to assess the severity of PSP-related clinical features, the PSP Saccadic Impairment Scale (PSIS) [25] to assess eye movement abnormalities, the Movement Disorders Society-sponsored revision of the Unified Parkinson's Disease Rating Scale Parts (UPDRS-I, UPDRS-II, and UPDRS-III) [26] to assess motor and non-motor functions, the Apraxia subscale of the WAB [23] to assess limb ideomotor apraxia, the Montreal Cognitive Assessment battery (MoCA) [23] to assess general cognition, the Frontal Behavioral Inventory (FBI) [27] to assess behavioral dyscontrol, and Trail Making Test A (TRAILS-A) [28] to assess visuomotor speed. A patient was judged to have Parkinsonism if bradykinesia plus an additional extrapyramidal feature (rigidity, postural instability, or resting tremor) was present.

All probable PSP ($n = 15$) and CBS ($n = 8$) patients included in our study were seen clinically or for research purposes in the Department of Neurology, Mayo Clinic, Rochester, MN, by a movement disorder or behavioral specialist (KAJ, HB, and FA) and had undergone DAT scan between January 1st 2012 and October 31st 2019. A DAT scan was performed in these patients to assess for confirmatory evidence of striatal abnormality.

Imaging

^{123}I-FP-CIT scans (DAT scan, GE Healthcare, Chicago, IL) were acquired using a 5 mCi ($\pm 10\%$) dose in a GE Tandem Optima SPECT scanner equipped with a fan-beam collimator (GE Healthcare, Chicago, IL). After images were acquired, they were then reconstructed through the ordered subset expectation maximization (OSEM) method. No attenuation correction was used. In a recent clinico-pathological study in which patients had been scanned using fan-beam collimators prior to death, we found an area under the receiving operator curve (AUROC) value of 0.97 for DaTQUANT to discriminate between patients with and without a neurodegenerative disease involving the striatum [29]. Age-corrected *Z*-scores and quantifying the uptake of ^{123}I-FP-CIT and striatum to background ratios (SBRs) for all striatal regions were individually calculated by DaTQUANT software, version 4.4, using a GE Healthcare Advantage Workstation. Results were obtained separately for the left and right anterior and posterior putamen and left and right caudate nucleus. Striatum to background ratios were utilized to calculate a putamen/caudate mean uptake ratio for the right and left anterior and posterior regions and absolute differences between the right and left striatal regions to reflect the degree of asymmetry across hemispheres. The image selection and *Z*-score calculation for all patients were implemented by the same version of DaTQUANT. Although

there is no definitely established threshold for abnormality, we selected a *Z*-score cutoff value of − 1.5 to determine whether uptake was abnormal in at least one striatal region for the PAOS patients. In addition, for all 17 PAOS patients, a nuclear medicine specialist visually rated the DAT scans as being abnormal or normal, independent of the *Z*-score cut-point determination of abnormal.

Approvals

The study was approved by the Mayo Clinic Institutional Review Board (IRB approval number: 17-002468). All patients signed a written informed consent before taking part in any research activities in accordance with the 1964 declaration of Helsinki and its later amendments.

Statistical analyses

Analyses were performed in JMP version 14 (SAS Institute, Cary, North Carolina, United States). Categorical data were summarized as counts and percentages, and continuous data were summarized as median and interquartile ranges (IQR). Statistical comparisons between two groups were performed using non-parametric Fisher's exact and Wilcoxon rank sum tests conservatively assuming non-normalcy of the data. For comparison across more than two groups, we used the non-parametric Steel–Dwass–Critchlow–Fligner test to correct for multiple comparisons. The PAOS group was divided into those with normal DAT scan uptake in all striatal regions (PAOS−) and those with abnormal DAT scan uptake in at least one striatal region (PAOS+). Demographic and clinical variables, and DAT scan results, were compared between PAOS− and PAOS+ groups, as well as between PAOS−, PAOS+, PSP and CBS. Alpha was set at $p < 0.05$.

Results

Of the 17 PAOS patients, 8 (47%) were male with the median age at onset of 70 years [interquartile range (IQR) 63–73] and disease duration (onset to scan) of 3 years (IQR 1.5–5) (Table 1). Of the 15 PSP patients, 6 (40%) were male with median age at onset of 64 years (IQR 56–66) and disease duration of median 2 years (IQR 1–3). Of the eight CBS patients, two (25%) were male with median age at onset of

Table 1 Baseline demographic and clincial characteristics of the PAOS patients

Variables	All PAOS ($n=17$)	PAOS− ($n=12$)	PAOS+ ($n=5$)	p value
Sex [M]	8 (47%)	3 (25%)	5 (100%)	0.005*
Handedness [R]	16 (94%)	12 (100%)	4 (80%)	0.11
Education, years	16 (13–18)	16 (12.5–17.5)	16 (12.5–19)	0.55
Age at onset, years	70 (63–73)	70 (62.5–73)	65 (55–78)	0.83
Age at DAT scan, years	73 (64–75)	73 (63–75)	69 (61–81)	0.75
Disease duration, years	3 (1.5–5)	3 (1–5)	4 (1.5–7)	0.53
UPDRS-I/52	7 (3.5–8)	6 (4–8)	7 (1.5–10.5)	0.96
UPDRS-II/52	3 (2.5–7)	3 (2.25–7.25)	4 (2.5–8)	0.67
UPDRS-III/132	11 (9–21.5)	11.5 (10–22.75)	11 (6.5–19.5)	0.56
FBI/72	10 (7.5–19.5)	9 (6.25–11.75)	18 (10.5–26)	0.10
Limb apraxia score/60	58 (52–59)	58 (51.5–58)	59 (53.5–59)	0.33
TRAILS-A MOANS	8 (6–11.75)	8 (6–11.75)	7.5 (4.5–12)	0.85
ASRS-3 total	19 (11–23.75)	14 (10–24)	23 (14–23.5)	0.5
Aphasia	12 (71%)	8 (67%)	4 (80%)	0.58
AOS type (phonetic/prosodic)[#]	7(41%)/4(24%)	5(42%)/3(25%)	2 (40%)/1(20%)	0.96
MoCA/30	25 (19–26)	24 (19–27)	25 (18–28)	0.91
WAB-AQ/100	96 (92.5–97.6)	95 (92.5–97.5)	97 (81–99)	0.4
PSIS/5	1 (0–1)	0.5 (0–1)	1 (0.5–1.5)	0.3
PSP-RS/100	12 (7–17)	11 (7–18.5)	12 (6–19.5)	0.9
PSP-GM/20	1 (0–3)	1 (0–2.75)	0 (0–3.5)	0.8

Data for sex, handedness, aphasia, and AOS type summarized as numbers (percentages) and for all other variables summarized as median (interquartile ranges). [M] represents male sex

PAOS− means PAOS patients with normal DAT scan, PAOS+ means PAOS patients with abnormal DAT scan

*Statistically significant

[#]Remaining cases had mixed features of both prosodic and phonetic

65 years (IQR 55–78) and disease duration of 3 years (IQR 1.5–8) (Table 2).

In the 17 PAOS patients, 5 showed reduced striatal radioisotope binding on the DAT scan. Three (60%) showed lower uptake in both anterior and posterior putamen, one showed lower uptake only in the left posterior putamen and one only in the left anterior putamen. Caudate uptake was also abnormal in one of the patients who showed both anterior and posterior putamen involvement.

When SBR values for all 17 PAOS patients were compared to the 15 PSP patients, the PSP group showed lower radioisotope uptake throughout the striatum on both sides ($p < 0.001$ for all regions). However, when the 17 PAOS patients were compared to the eight CBS patients, there were no significant differences in any region.

When the 12 PAOS− patients were compared to the 5 PAOS+ patients, the latter group showed significantly lower uptake in the left anterior and posterior putamen ($p = 0.01$ and $p = 0.05$) (Table 2). For the remaining striatum, there was no significant difference between the two groups. Although not statistically significant, PAOS− tended to have higher uptake throughout the striatum than PAOS+ (Table 2) (Fig. 1). PAOS− patients had significantly higher SBRs than PSP patients in all basal ganglia regions ($p < 0.001$ for all). However, there was no significant difference compared to the CBS patients in all striatal regions, except right caudate ($p = 0.03$). When putamen/caudate ratios of PAOS+ patients were compared to PAOS−, there were no significant differences across the groups for the right and left anterior and posterior putamen. Right–left absolute differences in the anterior and posterior putamen and caudate of PAOS+ group were not different from PAOS− (Table 2).

When SBR values in the five PAOS+ patients were compared to PSP and CBS, only the left posterior putamen ($p = 0.03$) had lower uptake in the PSP group compared to the PAOS+ group. No significant differences were observed between PAOS+ and CBS (Table 2). Even though not statistically significant, PSP patients in general tended to have the lowest uptake in all striatal regions compared to PAOS+ and to CBS (Table 2) (Fig. 1). There were also

Table 2 Comparison of demographic and DAT measures in PAOS, CBS, and PSP patients

Variables	PAOS− ($n = 12$)	PAOS+ ($n = 5$)	CBS ($n = 8$)	PSP ($n = 15$)	PAOS+ vs. PAOS− p value	PAOS+ vs. CBS p value	PAOS+ vs. PSP p value
Sex [M]	3 (25)	5 (100)	2 (25)	6 (40)	0.04*	0.07	0.12
Age at onset, years	70 (62.5, 73)	65 (55, 78)	54 (49, 62)	64 (56, 66)	1	0.50	0.82
Age at DAT scan, years	73 (63, 75)	69 (61, 81)	60 (57, 64)	66 (62, 71)	0.99	0.41	0.72
Disease duration, years	3 (1, 5)	4 (1.5, 7)	3 (1.5, 8)	2 (1, 3)	0.94	0.99	0.86
Right anterior putamen	1.89 (1.73, 2.42)	1.33 (0.88, 1.73)	1.57 (0.90, 1.82)	0.82 (0.60, 1.08)	0.08	0.99	0.22
Left anterior putamen	1.8 (1.62, 2.40)	1.30 (0.97, 1.44)	1.55 (1.05, 2.1)	0.8 (0.50, 0.94)	0.01*	0.70	0.07
Right posterior putamen	1.70 (1.38, 2.28)	1.21 (0.66, 1.50)	1.36 (0.53, 1.70)	0.59 (0.35, 0.70)	0.17	0.99	0.10
Left posterior putamen	1.68 (1.42, 2.33)	1.04 (0.90, 1.18)	1.25 (0.63, 1.91)	0.42 (0.30, 0.56)	0.05*	0.98	0.03*
Right caudate	2.63 (2.2, 2.70)	1.48 (1.40, 2.30)	1.94 (1.11, 2.13)	1.24 (0.75, 1.55)	0.17	0.99	0.18
Left caudate	2.25 (2.10, 2.64)	1.73 (1.42, 2.17)	1.86 (1.54, 2.54)	1.18 (0.70, 1.29)	0.13	0.91	0.08
Right anterior putamen/caudate ratio	0.84 (0.75, 0.88)	0.73 (0.62, 0.84)	0.82 (0.78, 0.87)	0.71 (0.60, 0.83)	0.55	0.69	0.99
Left anterior putamen/caudate ratio	0.80 (0.76, 0.90)	0.75 (0.57, 0.83)	0.79 (0.68, 0.84)	0.71 (0.61, 0.78)	0.42	0.85	0.99
Right posterior putamen/caudate ratio	0.72 (0.63, 0.85)	0.57 (0.47, 0.81)	0.70 (0.46, 0.82)	0.48 (0.31, 0.67)	0.55	0.96	0.90
Left posterior putamen/caudate ratio	0.79 (0.66, 0.85)	0.58 (0.46, 0.80)	0.65 (0.41, 0.76)	0.43 (0.31, 0.70)	0.68	0.99	0.61
Anterior putamen absolute difference	0.12 (0.08, 0.26)	0.27 (0.24, 0.37)	0.12 (0.03, 0.23)	0.12 (0.08, 0.19)	0.23	0.14	0.10
Posterior putamen absolute difference	0.13 (0.04, 0.18)	0.34 (0.22, 0.41)	0.14 (0.03, 0.32)	0.18 (0.07, 0.35)	0.06	0.41	0.26
Caudate absolute difference	0.28 (0.12, 0.32)	0.24 (0.13, 0.37)	0.29 (0.05, 0.53)	0.16 (0.11, 0.23)	0.96	0.88	0.22

Data for sex summarized as numbers (percentages) and for all other variables summarized as median (interquartile ranges). [M] represents the male sex

PAOS− means PAOS patients with normal DAT scan, PAOS+ means PAOS patients with abnormal DAT scan

*Statistically significant

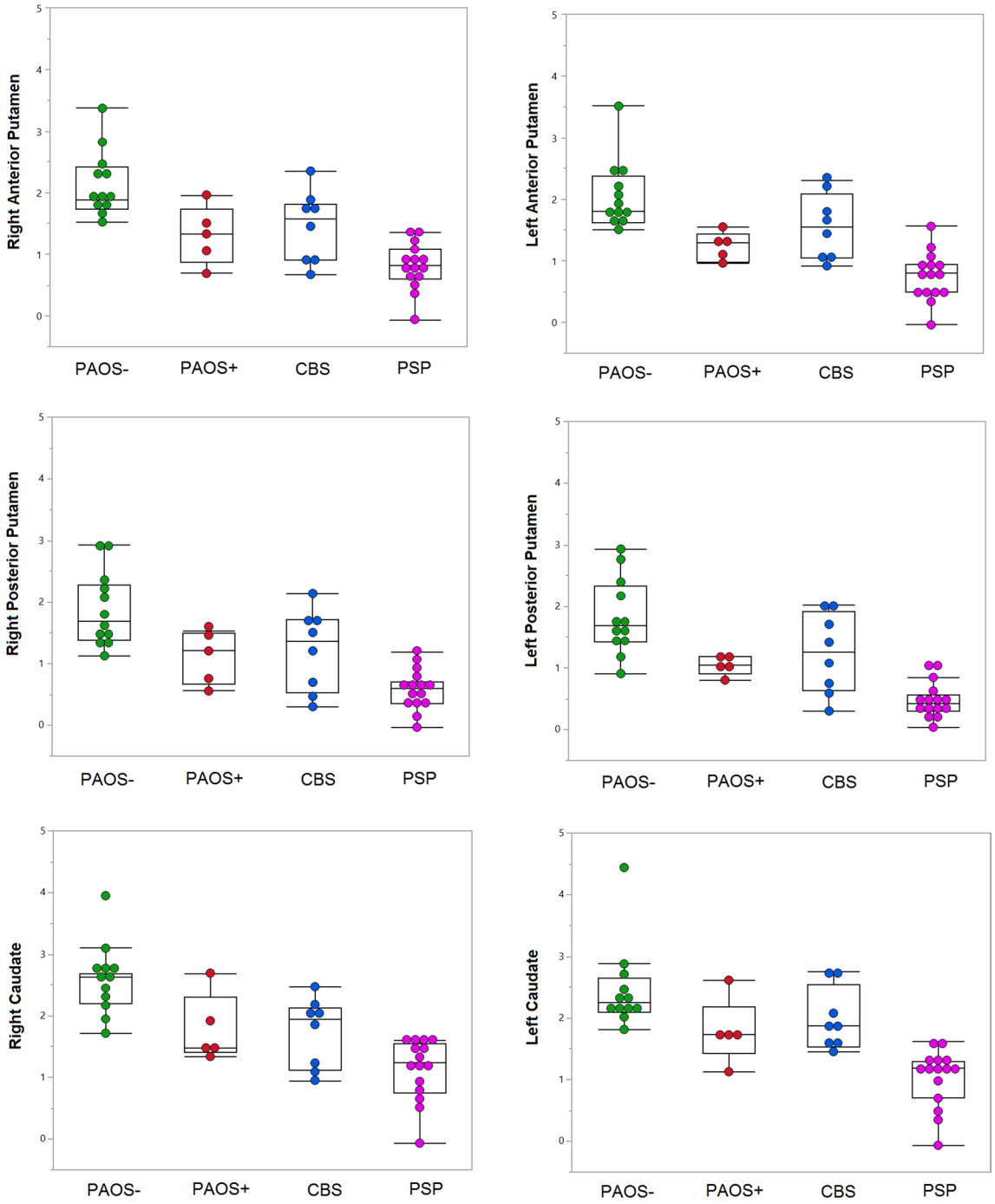

Fig. 1 Box plots demonstrate the greatest and the lowest striatum to background ratios (SBRs), lower quartile (25th percentile), upper quartile (75th percentile), and median SBR values for each group. Each dot represents each patient

no significant differences for putamen/caudate ratios or for absolute asymmetry between PAOS+ and both PSP and CBS (Table 2). Representative DAT scans for all four groups of patients are shown in Fig. 2.

The only difference in baseline clinical characteristic features was sex. The PAOS+ group had a higher proportion of men compared to the PAOS− group ($p = 0.005$) (Table 1). No differences were observed between the PAOS+ and PAOS− groups for any of the other clinical measures, including total MDS-UPDRS-III scores ($p = 0.56$) (Table 1). Mild and mild–moderate bradykinesia was observed in 7 of 17 PAOS patients (41%) at baseline visit. Of these seven patients, two were PAOS+ (40%) and five were PAOS− (41%). Rigidity was observed in 2 of the 17

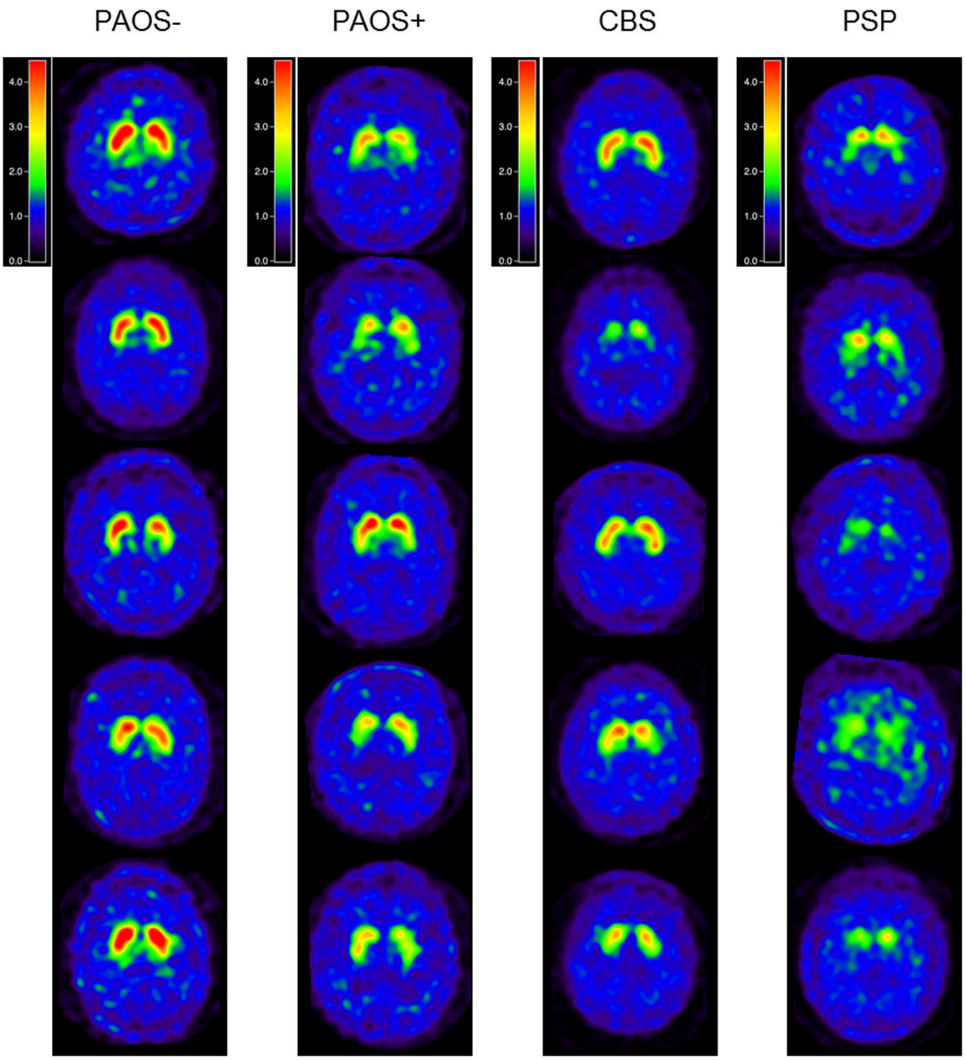

Fig. 2 DAT scan images from five representative PAOS+, CBS and PSP patients normalized to the occipital value. Note the severe loss of striatal uptake in some PSP patients compared to loss in the PAOS+ and CBS patients

PAOS patients (12%), one being PAOS+ the other PAOS−. Mild postural instability was observed in one patient. None of our PAOS patients had resting tremor. In total, three patients demonstrated mild clinical parkinsonism of which one was PAOS+ (20%) (Table 3).

Discussion

In this study, we found that almost a third of PAOS patients have an abnormal DAT scan and hence abnormal presynaptic dopamine transporter function. We found little difference in striatal uptake abnormality between PAOS patients with DAT abnormalities and patients with PSP and CBS. There appeared to be a dissociation between MDS-UPDRS-III scores and DAT scan abnormalities, in PAOS.

Five of the 17 PAOS patients had abnormalities in at least one striatal region on the DAT scan, demonstrating that DAT abnormalities are indeed observed in this population. DAT scan abnormalities of the five PAOS+ patients were not very different from the PSP and CBS patients. This is not surprising given that most PAOS patients progress over time and develop parkinsonism with features that overlap with those of PSP and CBS [2, 8, 9]. We did note, however, a trend for the PSP patients to have the lowest striatal uptake of all the groups, with significantly lower uptake observed in the left posterior putamen. There was no significant difference in SBR values between PAOS+ and CBS in any of the striatal regions and there was no trend for CBS to show less receptor binding. Hence, the PAOS+ patients appeared slightly more similar to CBS than PSP. Our PAOS patients with abnormal DAT scans showed similar involvement of both anterior and posterior putamen, as has also been observed in PSP [30] and CBS [31]. Furthermore, the PAOS+ patients did not demonstrate significantly more asymmetry than CBS and PSP. CBS has been found to be more asymmetric when compared to normal controls, but not when compared to PSP [12]. Hence, it not surprising that PAOS was not any more

Table 3 Parkinsonian signs on examination in all 17 PAOS patients

Clinical features	DAT scan status	Bradykinesia	Rigidity	Postural instability	Resting tremor	Parkinsonism
Patients						
1[¥]	−	Yes	No	No	No	No
2	−	No	No	No	No	No
3	−	No	No	No	No	No
4	−	No	No	No	No	No
5	−	No	No	No	No	No
6[β]	−	Yes	No	Yes	No	Mild
7	−	No	No	No	No	No
8[Φ]	−	Yes	No	No	No	No
9	−	No	No	No	No	No
10[Ω]	−	Yes	Yes	No	No	Mild
11	−	No	No	No	No	No
12[β]	−	Yes	No	No	No	No
13	+	No	No	No	No	No
14	+	No	No	No	No	No
15[β]	+	Yes	No	No	No	No
16	+	No	No	No	No	No
17[Ω]	+	Yes	Yes	No	No	Mild

Parkinsonism is determined by the presence of bradykinesia plus one of the other clinical features (rigidity, postural instability, and resting tremor)

[¥]Bradykinesia restricted to lower extremities of mild–moderate severity

[β]Bradykinesia mild–moderate in upper extremities and mild in lower extremities

[Ω]Bradykinesia mild–moderate in the upper extremities, mild in the lower extremities and mild rigidity in the upper extremities

[Φ]Bradykinesia mild in the upper extremities only

or less asymmetric when compared to PSP and CBS. We did not find the putamen/caudate ratio to be helpful to differentiate the PAOS+ group from any other group, including the PAOS− group. As expected the PAOS+ patients showed lower uptake, with a trend for uptake to be more asymmetric, compared to the PAOS− patients.

Given the mechanism of DAT abnormalities in Parkinson disease, it appears that early striatal dysfunction is a feature of some PAOS patients. However, only one of the PAOS+ patients was clinically considered to have Parkinsonism and the PAOS+ patients with abnormal DAT scans did not demonstrate more Parkinsonism on the MDS-UPDRS-III scale compared to the PAOS− patients. Hence, it would appear that DAT scan is a more sensitive detector of early striatal abnormalities in PAOS compared to clinical examination. DAT scan has also been found to be an early marker of Parkinsonism in patients with rapid eye movement sleep behavior disorder who later developed an alpha-synucleinopathy [32].

Somewhat unexpectedly, the PAOS+ patients with abnormal DAT scans did not demonstrate more Parkinsonism on the MDS-UPDRS-III scale compared to the PAOS− patients. Similarly, the proportion of patients who demonstrated clinical Parkinsonism was almost equal for both the PAOS− and PAOS+ groups. This brings up the issue of patients diagnosed with idiopathic Parkinson's disease without evidence of dopaminergic deficit (SWEDD). Such patients were later found to have alternative clinical diagnoses [33–35]. One of the reasons for an absence of association in our PAOS cohort was that three of the PAOS− patients had high MDS-UPDRS-III scores [range 24–36]. This result indicates that the high MDS-UPDRS-III scores in these three patients do not reflect involvement of the presynaptic dopamine transporters. Hence, other causes of elevated scores needed to be explored. On review of MRI imaging studies in these three patients, there was no evidence of normal pressure hydrocephalus or vascular pathology. There was also no evidence for drug-induced Parkinsonism in the medical records, psychogenic Parkinsonism, or other metabolic causes to explain the high MDS-UPDRS-III scores and the normal DAT scans. There was also no difference in limb praxis measures that could have affected performance on the MDS-UPDRS-III. In looking at the individual MDS-UPDRS-III scores in these three PAOS− patients it appears that the higher scores were driven mainly by bradykinetic alternating motion rates of the limbs, yet without motor arrest. We hypothesize that bradykinetic phenomenon in PAOS could reflect cortical involvement. This hypothesis is predicated on the fact that

some PAOS patients have AOS characteristics of predominantly slow and segmented speech known as AOS type 2 [36] or prosodic AOS [37]. Such patients with slowed speech show involvement of the medial and lateral premotor cortex on neuroimaging measures including MRI and [^{18}F] fluorodeoxyglucose PET scans [5, 37]. Future studies are needed to test this hypothesis.

There are a few limitations of this study including the cross-sectional study design. We are, however, currently following all 17 PAOS patients and in the future will be able to determine how the DAT scan and MDS-UPDRS-III scores and relationships between them evolve. Another limitation is the lack of pathological diagnosis of patients in the cohort. Third, our sample size was relatively small. Lastly, we did not have a normal control group with fan-beam collimators as a comparison group.

Conclusion

Abnormal DAT scan can be observed early in the disease course in approximately 30% of PAOS patients, with abnormalities similar to those observed in PSP and CBS. DAT scan, therefore, has potential as an early diagnostic measure of impaired dopamine transporter integrity that might be more sensitive than clinical measures including the MDS-UPDRS-III scale.

Author contributions ZIS, JLW and KAJ have full access to all data, and take responsibility for the accuracy of the data analyses and interpretation. FA contributed to patient recruitment. All authors contributed to the study concept and design, discussed the data results, contributed to drafting of the manuscript and approved the final version for submission. KAJ is the guarantor of the paper.

Funding This project is funded by NIH Grants R01 DC14942 and R01 DC12519.

Compliance with ethical standards

Conflicts of interest No conflicts exist for any of the authors.

References

1. McNeil MR, Robin DA, Schmidt RA (2009) Apraxia of speech: definition and differential diagnosis. Clin Manag Sens Speech Disord 2:249–267
2. Josephs KA et al (2014) The evolution of primary progressive apraxia of speech. Brain 137(10):2783–2795
3. Duffy JR (2006) Apraxia of speech in degenerative neurologic disease. Aphasiology 20(6):511–527
4. Josephs KA et al (2005) Atypical progressive supranuclear palsy underlying progressive apraxia of speech and nonfluent aphasia. Neurocase 11(4):283–296
5. Josephs KA et al (2012) Characterizing a neurodegenerative syndrome: primary progressive apraxia of speech. Brain 135(5):1522–1536
6. Josephs KA et al (2006) Clinicopathological and imaging correlates of progressive aphasia and apraxia of speech. Brain 129(6):1385–1398
7. Whitwell JL et al (2019) An evaluation of the progressive supranuclear palsy speech/language variant. Mov Disord Clin Pract 6(6):452–461
8. Tetzloff KA et al (2018) Clinical and imaging progression over 10 years in a patient with primary progressive apraxia of speech and autopsy-confirmed corticobasal degeneration. Neurocase 24(2):111–120
9. Utianski RL et al (2018) Clinical progression in four cases of primary progressive apraxia of speech. Am J Speech Lang Pathol 27(4):1303–1318
10. Marshall VL et al (2009) Parkinson's disease is overdiagnosed clinically at baseline in diagnostically uncertain cases: a 3-year European multicenter study with repeat [123I]FP-CIT SPECT. Mov Disord 24(4):500–508
11. Seifert KD, Wiener JI (2013) The impact of DaTscan on the diagnosis and management of movement disorders: a retrospective study. Am J Neurodegener Dis 2(1):29–34
12. Pirker W et al (2000) [123I]beta-CIT SPECT in multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration. Mov Disord 15(6):1158–1167
13. Klaffke S et al (2006) Dopamine transporters, D2 receptors, and glucose metabolism in corticobasal degeneration. Mov Disord 21(10):1724–1727
14. Im JH et al (2006) Differential patterns of dopamine transporter loss in the basal ganglia of progressive supranuclear palsy and Parkinson's disease: analysis with [(123)I]IPT single photon emission computed tomography. J Neurol Sci 244(1–2):103–109
15. McKhann G et al (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34(7):939–944
16. McKeith IG et al (2005) Diagnosis and management of dementia with Lewy bodies: third report of the DLB consortium. Neurology 65(12):1863–1872
17. Neary D et al (1998) Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 51(6):1546–1554
18. Litvan I et al (1996) Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele–Richardson–Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 47(1):1–9
19. Boeve BF, Lang AE, Litvan I (2003) Corticobasal degeneration and its relationship to progressive supranuclear palsy and frontotemporal dementia. Ann Neurol 54(5):S15–S19
20. Gilman S et al (2008) Second consensus statement on the diagnosis of multiple system atrophy. Neurology 71(9):670–676
21. Brooks BR et al (2000) El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 1(5):293–299
22. Duffy JR, Strand EA, Josephs KA (2014) Motor speech disorders associated with primary progressive aphasia. Aphasiology 28(8–9):1004–1017
23. Nasreddine ZS et al (2005) The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 53(4):695–699
24. Hoglinger GU et al (2017) Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. Mov Disord 32(6):853–864
25. Whitwell JL et al (2011) Clinical correlates of white matter tract degeneration in progressive supranuclear palsy. Arch Neurol 68(6):753–760

26. Goetz CG et al (2008) Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 23(15):2129–2170
27. Kertesz A, Davidson W, Fox H (1997) Frontal behavioral inventory: diagnostic criteria for frontal lobe dementia. Can J Neurol Sci 24(1):29–36
28. Strauss SA (1998) An unusual case of wrongful pregnancy: liability of doctor resulting from misrepresentation. Med Law 17(1):7–11
29. Maltais DD et al (2020) Confirmation of (123)I-FP-CIT-SPECT (ioflupane) quantification methods in dementia with Lewy body and other neurodegenerative disorders. J Nucl Med 2020:119
30. Antonini A et al (2003) 123I-Ioflupane/SPECT binding to striatal dopamine transporter (DAT) uptake in patients with Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. Neurol Sci 24(3):149–150
31. Badoud S et al (2016) Discriminating among degenerative parkinsonisms using advanced (123)I-ioflupane SPECT analyses. Neuroimage Clin 12:234–240
32. Iranzo A et al (2017) Dopamine transporter imaging deficit predicts early transition to synucleinopathy in idiopathic rapid eye movement sleep behavior disorder. Ann Neurol 82(3):419–428
33. Stephenson D et al (2019) The qualification of an enrichment biomarker for clinical trials targeting early stages of Parkinson's disease. J Parkinsons Dis 9(3):553–563
34. Nicastro N, Burkhard PR, Garibotto V (2018) Scan without evidence of dopaminergic deficit (SWEDD) in degenerative parkinsonism and dementia with Lewy bodies: a prospective study. J Neurol Sci 385:17–21
35. Marek K et al (2014) Longitudinal follow-up of SWEDD subjects in the PRECEPT study. Neurology 82(20):1791–1797
36. Josephs KA et al (2013) Syndromes dominated by apraxia of speech show distinct characteristics from agrammatic PPA. Neurology 81(4):337–345
37. Utianski RL et al (2018) Prosodic and phonetic subtypes of primary progressive apraxia of speech. Brain Lang 184:54–65