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Short Communications

Longitudinal changes in dopamine transporter uptake scans in progressive apraxia of speech

Rene L. Utianski [a,*], Nha Trang Thu Pham [b], Hugo Botha [a], Farwa Ali [a], Joseph R. Duffy [a], Heather M. Clark [a], Val J. Lowe [c], Jennifer L. Whitwell [c], Keith A. Josephs [a]

[a] Departments of Neurology, and, Mayo Clinic, Rochester, MN, USA
[b] Health Sciences Research, and, Mayo Clinic, Rochester, MN, USA
[c] Radiology and, Mayo Clinic, Rochester, MN, USA

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ABSTRACT

Purpose: To describe qualitative and quantitative longitudinal changes in dopamine transporter uptake (DaT) scan findings in progressive apraxia of speech (PAOS) patients.
Methods: DaTQUANT software was used to quantify uptake in the left and right caudate and putamen in DaT scans of 39 patients with PAOS, 19 with repeat scans. Clinical radiologic impressions were used as the gold standard for evaluating whether quantitative measures (z-score of left and right putamen and caudate uptake) aligned with gestalt impressions of DaT abnormalities and clinical impairments, cross-sectionally. Measures at first and last available DaT were used to evaluate change over time and the influence of qualitative abnormality at first visit on change over time.
Results: Cross-sectionally, 16/39 patients had abnormal DaT scans on visual read, with differences in all quantitative DaT measures between those with (ab)normal scans, but without differences in any clinical measures (apraxia of speech, aphasia, or parkinsonism). Three patients that had normal DaT scans at baseline were read as abnormal at subsequent visits, with coinciding change in quantitative measures. At the group level, across the 19 patients with repeat imaging, no statistical change in left or right caudate or putamen scores was observed despite progression of clinical indices. Abnormality at first visit did not statistically influence the rate of change over time, although trends were observed.
Conclusions: Approximately 40–50% of patients with PAOS have or will develop DaT scans that may be visually read as abnormal. Quantitative measures of DaT match visual reads cross-sectionally, but may not map to clinical progression, including of parkinsonism, observed in these patients.

1. Introduction

Apraxia of speech (AOS) that results from neurodegeneration is referred to as progressive AOS (PAOS) [1]. Research has shown that patients with PAOS develop parkinsonism, ultimately developing a progressive supranuclear palsy (PSP)- corticobasal syndrome (CBS) overlap syndrome [2] with the associated pathologies at autopsy [3]. The clinical course and specific pathology may be dictated by the predominance of phonetic or prosodic speech features at onset [4,5]. There is some evidence to suggest that cortical dysfunction may predominate in phonetic PAOS, while subcortical and brainstem dysfunction may predominate in prosodic PAOS [4].

On ioflupane ^{123}I-FP-CIT dopamine transporter (DaT) SPECT, past studies have demonstrated an association between decreased striatal dopamine binding and extrapyramidal features amongst parkinsonian syndromes [6–8]. Abnormal dopamine binding has also been reported in patients with PAOS [9–11]; one study showed 30% of patients with PAOS had involvement of the nigrostriatal dopaminergic system. It remains unclear if this is a direct reflection of loss of dopaminergic neurons or secondary to disruption amongst the associated cortical-subcortical circuits.

While the practice standard to determine DaT abnormalities is visual qualitative judgments, this is often supplemented by objective, quantified measures. Given the lack of widely available, objective markers of disease progression for PAOS, the aim of this study was to evaluate longitudinal change in DaT scans in patients with PAOS. Specifically, we

* Corresponding author at: Department of Neurology, Mayo Clinic, 200 1st Street, SW, Rochester, MN 55904, USA
E-mail address: Utianski.Rene@mayo.edu (R.L. Utianski).

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Table 1
Demographics of cross-sectional and longitudinal data, presented as median (interquartile range).

Characteristic	Abnormal, N = 16[1]	Normal, N = 23[1]	p-value[2]	First visit, N = 19[1]	Last visit, N = 19[1]	p-value[2]
Encounter age (years)	69.8 (64.6, 76.9)	72.9 (64.7, 76.0)	0.944	72.9 (63.1, 77.6)	74.8 (64.6, 79.8)	0.488
Age at onset (years)	67.0 (60.5, 75.1)	68.8 (62.5, 72.5)	0.883	70.4 (62.1, 74.2)		
Disease duration (years)	3.4 (2.4, 6.1)	2.6 (1.9, 5.1)	0.235	3.8 (2.0, 5.1)		
Gender, Male	12 (75%)	8 (35%)	**0.013**	8 (42%)		
AOS type			0.773			>0.999
Mixed	4 (25%)	5 (22%)		2 (11%)	2 (11%)	
Phonetic	7 (44%)	8 (35%)		8 (42%)	8 (42%)	
Prosodic	5 (31%)	10 (43%)		9 (47%)	9 (47%)	
Right Putamen z- score	−1.1 (−2.6, −0.2)	0.5 (−0.3, 1.2)	**<0.001**	−0.5 (−1.2, 0.4)	−0.4 (−2.0, −0.3)	0.579
Left Putamen z- score	−1.6 (−2.3, −1.0)	0.3 (−0.2, 1.0)	**<0.001**	−0.4 (−1.4, 0.3)	−1.0 (−2.1, 0.0)	0.255
Right Caudatus z- score	−0.6 (−1.5, 0.5)	1.0 (0.2, 1.4)	**0.004**	0.6 (−0.9, 1.1)	−0.4 (−1.3, 1.0)	0.456
Left Caudatus z- score	−0.6 (−0.9, −0.1)	0.5 (−0.1, 1.2)	**0.003**	0.3 (−0.5, 0.7)	−0.3 (−1.2, 0.6)	0.414
ASRS total (/52)	22.0 (11.8, 25.0)	20.0 (12.5, 23.5)	0.830	23.0 (13.5, 24.0)	32.0 (27.0, 35.0)	**<0.001**
ASRS phonetic (/16)	7.0 (4.0, 10.5)	6.0 (4.0, 8.0)	0.349	7.0 (4.0, 9.5)	11.0 (8.0, 14.0)	**0.015**
ASRS prosodic (/16)	6.0 (4.8, 10.0)	7.0 (3.5, 11.0)	0.875	9.0 (4.0, 10.5)	11.0 (7.0, 13.0)	**0.040**
WAB AQ (/100)	95.7 (89.5, 98.5)	97.0 (93.4, 98.3)	0.587	97.0 (93.6, 98.0)	89.0 (83.7, 94.4)	**0.015**
UPDRS III (/120)	15.0 (6.5, 22.5)	12.0 (9.5, 20.0)	0.869	12.0 (9.0, 20.0)	20.0 (16.0, 27.5)	**0.025**
MoCA (/30)	23.0 (20.0, 25.5)	25.0 (21.0, 27.0)	0.470	25.0 (20.0, 27.0)	18.0 (13.5, 24.5)	**0.021**

sought to 1) describe the proportion of patients with abnormal DaTscans at baseline and follow-up, 2) evaluate whether qualitative judgments and/or quantitative measurements of DaTscan uptake in striatal regions (caudate and putamen) change over time in PAOS, and 3) determine if there is a difference in rate of change in uptake between patients with qualitatively normal or abnormal DaT scans at first visit.

2. Methods

2.1. Participants

Building upon those reported in a prior study [10], thirty-nine unique patients (20 male) with PAOS, not on dopaminergic treatment, were seen by the Neurodegenerative Research Group (NRG) at Mayo Clinic. While some patients had parkinsonism in addition to AOS, they did not meet criteria for possible or probable PSP or CBS. Nineteen patients had more than one visit, allowing for longitudinal evaluation of change. This study was approved by the Mayo Clinic Institutional Review Board and all patients provided written consent to participate. The study was carried out in accordance with the Declaration of Helsinki and responsible conduct for human subjects research.

2.2. Clinical examination

The speech and language evaluation included rating the Apraxia of Speech Rating Scale (ASRS-3) [12], to index the presence and prominence of speech features associated with AOS, and computing the Western Aphasia Battery- Revised Aphasia Quotient (WAB-AQ), to index aphasia presence and severity. Judgments regarding the presence and nature of AOS and aphasia were made by consensus between at least two board-certified speech-language pathologists based on reviewing video recordings of key portions of the speech and language examination. The neurological evaluation included completing the Movement Disorders Society-sponsored revision of the Unified Parkinson's Disease Rating Scale Parts (UPDRS-III) to assess motor function and the Montreal Cognitive Assessment battery (MoCA) to assess general cognition.

2.3. Imaging

Ioflupane ^{123}I-FP-CIT scans (DAT scan, GE Healthcare, Chicago, IL) were acquired using a 5 mCi (±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 reconstructed through the ordered subset expectation maximization method. No attenuation correction was used. Independent of the DaTQUANT calculations, a nuclear medicine specialist visually rated each DAT scan as being abnormal or normal, in line with standard clinical protocol. With input from two board-certified neurologists, consensus agreement was reached by review of the scans, and utilized as the qualitative judgment of abnormality for this study. Image selection and age-corrected z-scores were automatically calculated separately for the left and right putamen and left and right caudate nucleus with DaTQUANT software (version 4.4).

2.4. Data analyses

Analyses were performed in R statistical software. Categorical data were summarized as counts and percentages, and continuous data as median and interquartile ranges (IQR). Statistical comparisons between two groups were performed using non-parametric Fisher's Exact, Pearson's Chi-squared test, and Wilcoxon Rank sum tests conservatively assuming non-normalcy of the data. Demographic and clinical variables, and DaTQUANT results, were compared between radiology judged abnormal/ normal groups for cross-sectional data and first and last visit for longitudinal data, to evaluate aims one and two, respectively. Alpha was set at $p < 0.05$.

To evaluate the impact of qualitative ab/normality at first visit on change over time, annual change in DaT values for each individual and each region of interest was calculated as the difference in DaT values between the two scans divided by time between scans. Linear regression models with these annual change values as the outcome (y) and baseline radiologist impression of DaT scans as the predictor (x) were used to estimate mean differences in rates of DaT result across the two clinical groups for the four regions of interest.

3. Results

Clinical and demographic data for the cross-sectional and longitudinal cohorts are summarized in Table 1. The first aim was to describe the proportion of patients with abnormal DaTscans. In this cohort, 16/39 patients (41%) had abnormal DaT scans, with slightly more males represented. Cross-sectionally, there was no difference in age of onset, evaluation, or disease duration. There were differences in all DaTQUANT measures between the normal and abnormal groups, consistent with design. There were no differences in any clinical measures [ASRS-3 (AOS severity), WAB-AQ (language), or UPDRS III (parkinonism)], or proportion of AOS subtypes, between groups.

The second aim was to understand whether qualitative judgments and/or quantitative measurements of DaTscan uptake change over time in PAOS. In the cohort of 19 patients with longitudinal follow-up, three patients who had normal DaT scans at their first visit had abnormal scans on follow-up (with quantitative change in each region of interest;

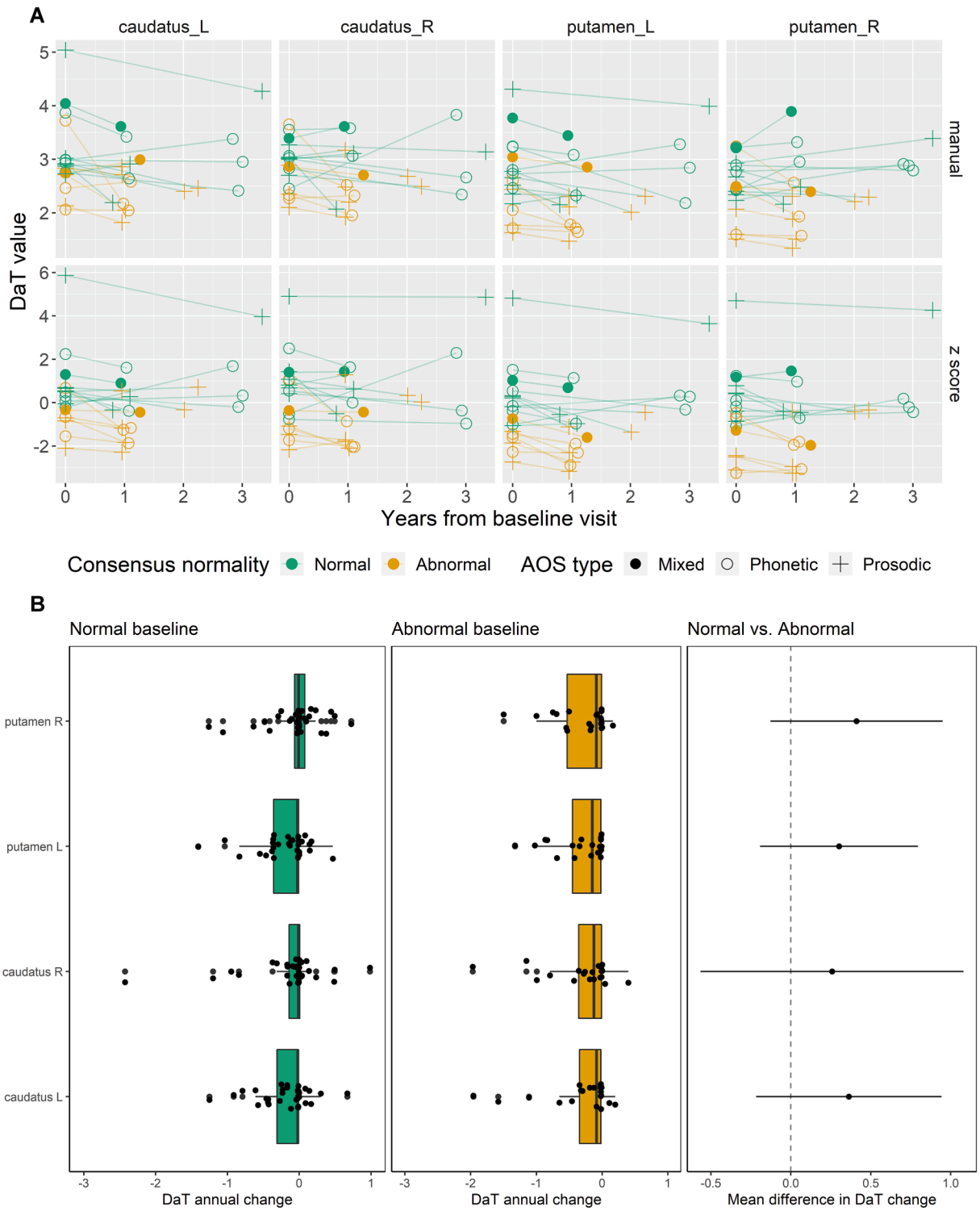

Fig. 1. A) (top) DaT z-scores for each individual patient with follow-up evaluation, where color reflects qualitative judgment (consensus normality) and shape indicates AOS subtype; **B) (bottom):** Evaluation of impact of baseline normality on change in quantitative measures over time.

see Fig. 1). At the group level, there was no significant change in caudate or putamen scores over time, which was a median of 1.9 years between scans. In contrast, progression was documented on all clinical measures of interest, including the ASRS-3, WAB-AQ, and UPDRS III scores. There was no statistically significant relationship between rate of change and abnormality at baseline.

4. Discussion

This is the first study to examine longitudinal quantitative and qualitative changes in DaT scans in patients with PAOS. In this cohort, 41% of patients had abnormal DaT scans, per visual read. Quantitative measures aligned with the qualitative judgments. The relationship with DaT abnormalities and type and location of the underlying pathology is of interest in future studies. Unexpectedly, there was no difference in

UPDRS III scores between those with normal versus abnormal DaT scans, as all patients had some features of parkinonism (as often seen in PAOS; [2]); however, there as progression noted between UPDRS III scores longitudinally.

In the cohort of 19 patients with longitudinal follow-up, seven were abnormal at first visit and an additional three (all prosodic predominant AOS) became abnormal. This may reflect greater involvement of the striatum and expected disruption of striatal dopamine uptake in prosodic AOS [4] although patients with prosodic AOS were not more likely to be abnormal cross-sectionally; this trend should be explored in a larger cohort. There were no differences in DaTQUANT measures between visits across the 19 patients with follow-up, which may reflect the small number of patients who transitioned from normal to abnormal; on the individual basis, the patients who qualitatively changed demonstrated decline on the quantitative measures. It appears that DaT measures of patients with postive DaT scans may change more than patients with initially negative DaT scans (Fig. 1), but this does not reach statistical significance. Further evaluation of whether imaging and clinical tests of patients with positive DAT scans progress more quickly is warranted in a larger sample. While the confidence in conclusions is tempered by the sample size and short interval evaluated, taken together, DaT scan measures (quantitative and qualitative) may be more sensitive at the cross-sectional versus longitudinal level, but do not always map onto symptoms of parkinonism in presumed 4R tauopathies. Importantly, prior research has shown sensitivity longitudinally for synucleinopathies [13].

In a prior study of seven patients with progressive nonfluent primary progressive aphasia, qualitative DaT progression suggested abnormalities may predict progression to parkinsonism [9,14] or worsening cognition, but we did not see this relationship with our selected measures (UPDRS, WAB-AQ, and MoCA). In our cohort, the statistical analyses supported progression of motor and cognitive symptoms (indexed by the UPDRS, WAB-AQ, and MoCA), without statistical change in quantitative DaT scores. Differing results could reflect heterogenous cohorts or different statistical analysis; such relationships should be further explored in larger cohorts.

While this study is the first to look at both quantitative and qualitive longitudinal change on DaT scans in patients with PAOS, it is not without limitations. First, there was no control group either for unimpaired patients or patients with related parkinsonian disorders, although a prior study suggested no differences exist cross-sectionally [10]. Second, this study examined change over a relatively short interval (median 1.9 years). It also did not evaluate change in symmetry indices, which could be informative given the presence of asymmetric motor symptoms in some patients with PAOS [5]. Neither manually defined regions of interest nor sensitivity and specificity were formally evaluated. Prior studies have shown different quantitative thresholds align with different clinical diagnoses [15], so this could be explored. No patients were on dopamanergic treatment, but future studies should continue to monitor the potential influence of such medication on results. Finally, the longitudinal cohort was small which limits the ability to confidently discern the relationship of AOS subtype and DaT changes.

CRediT authorship contribution statement

Rene L. Utianski: Conceptualization, Investigation, Methodology, Funding acquisition, Writing – original draft. **Nha Trang Thu Pham:** Methodology, Formal analysis, Visualization. **Hugo Botha:** Investigation, Writing – review & editing. **Farwa Ali:** Investigation, Writing – review & editing. **Joseph R. Duffy:** Investigation, Writing – review & editing. **Heather M. Clark:** Investigation, Writing – review & editing. **Val J. Lowe:** Investigation, Writing – review & editing. **Jennifer L. Whitwell:** Conceptualization, Methodology, Funding acquisition, Writing – review & editing. **Keith A. Josephs:** Methodology, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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