Received: 6 July 2023 | Accepted: 14 November 2023

DOI: 10.1111/ene.16169

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Abnormal dopamine transporter imaging in pure autonomic failure: a potential biomarker of central nervous system involvement

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Abstract

Background and purpose: Pure autonomic failure (PAF) is a rare progressive neurodegenerative disease characterized by neurogenic orthostatic hypotension at presentation, without other neurological abnormalities. Some patients may develop other central neurological features indicative of multiple system atrophy or a Lewy body disorder. There are currently no biomarkers to assess possible central nervous system involvement in probable PAF at an early stage. A possibility is to evaluate the nigrostriatal dopaminergic degeneration by imaging of dopamine transporter with DaTscan brain imaging. The objective was to evaluate subclinical central nervous system involvement using DaTscan in PAF.

Methods: We retreospectively reviewed pure autonomic failure patients who were evaluated at the Autonomic Unit between January 2015 and August 2021 and underwent comprehensive autonomic assessment, neurological examination, brain magnetic resonance imaging and DaTscan imaging. DaTscan imaging was performed if patients presented with atypical features which did not meet the criteria for Parkinson's disease or multiple system atrophy or other atypical parkinsonism.

Results: In this cohort, the median age was 49.5 years at disease onset, 57.5 years at presentation, and the median disease duration was 7.5 years. Five of 10 patients had an abnormal DaTscan without neurological features meeting the criteria of an alternative diagnosis. Patients with abnormal DaTscan were predominantly males, had shorter disease duration and had more severe genitourinary symptoms.

Discussion: Degeneration of nigrostriatal dopaminergic neurons measured using DaTscan imaging can present in patients with PAF without concurrent signs indicating progression to widespread α-synucleinopathy. It is advocated that DaTscan imaging should be considered as part of the workup of patients with emerging autonomic failure who are considered to have PAF.

KEYWORDS
central involvement, DaTscan, dopamine transporter, phenoconversion, pure autonomic failure

INTRODUCTION

Pure autonomic failure (PAF) is a rare neurodegenerative disorder characterized by autonomic failure resulting from α-synuclein accumulation in the autonomic ganglia and peripheral autonomic nerves with sparing of the central nervous system [1]. Patients usually present with autonomic failure characterized by neurogenic orthostatic hypotension (OH). There may also be gastrointestinal, genitourinary and thermoregulatory dysfunction symptoms and signs indicative of central nervous system dysfunction [2].

The diagnosis of PAF is currently based on consensus criteria published in May 1996 [3]. Autonomic testing typically demonstrates widespread cardiovascular autonomic failure with neurogenic OH, reduced heart rate (HR) variability, low plasma catecholamines and denervation super-sensitivity [1]. Postganglionic denervation, loss of noradrenergic and cholinergic autonomic nerves, and accumulation of α-synuclein have been observed in skin biopsies [4]. Phosphorylated α-synuclein deposition in skin sympathetic nerve fibres is found to be a sensitive biomarker of PAF [5].

Some patients with PAF may progress to a widespread α-synucleinopathy within 3–5 years of symptom onset, although patients with longstanding PAF features (>10 years of history) converting to a widespread α-synucleinopathy have also been described [4,6]. In PAF, the presence of early severe bladder dysfunction, rapid eye movement (REM) sleep behaviour disorder (RBD) and normal supine catecholamine levels may increase the probability of phenoconversion to either multiple system atrophy (MSA) or Lewy body disorder (LBD) [7].

Despite the predominantly peripheral pathology in PAF, central deposition of misfolded α-synuclein has been described in the basal ganglia and locus coeruleus without neuronal loss in some patients [4]. This raises the question of whether PAF represents isolated postganglionic and peripheral involvement of the autonomic nervous system or it is an early premotor phase of a widespread α-synuclein deposition such as MSA or LBD in a subgroup of patients [4, 7].

Metaiodobenzylguanidine (MIBG) imaging can reveal cardiac sympathetic denervation in patients with α-synucleinopathies including PAF and LBD. Positive MIBG imaging can predict the phenoconversion to MSA in the premotor phase [6]. LBD and MSA characteristically involve degeneration of the nigrostriatal dopaminergic neurons, and presynaptic dopamine transporter (DAT) concentration is typically reduced in these conditions. This presynaptic involvement can be detected by dopamine transported single-photon emission computed tomography (DaTscan) which measures the concentration of the presynaptic dopaminergic transporters using a radioactive isotope [8]. DaTscan can also predict subclinical Parkinson's disease (PD) up to 4 years before the clinical diagnosis [9].

Despite the high rate of phenoconversion to a more widespread α-synucleinopathy, there is a lack of prospective studies exploring the presence of a subclinical nigrostriatal dopaminergic loss in patients with well characterized PAF [10, 11].

A normal DaTscan was used to support the diagnosis of PAF in a study involved 44 patients with α-synucleinopathies; amongst them five patients were diagnosed with PAF based on clinical features, abnormal MIBG and normal DaTscan [12].

OBJECTIVES

The aim was to assess the potential evidence for nigrostriatal dopaminergic neuronal loss using a DaTscan as a biomarker of subclinical central nervous system degeneration in PAF patients.

METHODS

Patients assessed at the Autonomic Unit at the National Hospital for Neurology and Neurosurgery were investigated for suspected PAF between January 2015 and August 2021. PAF was defined as autonomic failure resulting in neurogenic OH in association with other autonomic dysfunction (gastrointestinal, urogenital and sudomotor dysfunction) in the absence of any neurological, metabolic, hereditary or toxic neuropathy [3].

Orthostatic hypotension was defined as a drop in systolic blood pressure (SBP) ≥20 mmHg or diastolic blood pressure (DBP) ≥10 mmHg on standing or tilt table tests [3]. Patients with evidence of peripheral neuropathy suggestive of amyloidosis, diabetes or autoimmune disease were excluded.

As part of the clinical workup, patients underwent autonomic cardiovascular function tests, serum catecholamine levels, ambulatory 24-h blood pressure (BP) monitoring, DaTscan, and magnetic resonance imaging (MRI) of the brain. DaTscan was perdormed in cases where patients presented with atypical features suggesting the possibility of emerging widespread α-synucleinopathy such as Lewy body disorders (PD and DLB) or MSA. Atypical features were defined as subtle neurological signs, such as incoordination, mild rigidity, mild tremor, or severe bladder dysfunction in the early stage of the disease, which did not meet the criteria for PD or MSA or other atypical parkinsonism.

Demographic details, age at onset of the orthostatic intolerance symptoms, presenting autonomic symptoms, other clinical features, age at autonomic assessment, disease duration at last assessment, autonomic cardiovascular investigation including BP, HR changes during standing and head-up tilt, orthostatic intolerance ratio (OIR) (defined as ΔSBP on head-up tilt divided by minutes of tilt tolerance), Valsalva ratio, respiratory sinus arrhythmia, serum catecholamine levels (supine and tilt), circadian rhythm during 24-h BP monitoring, and the presence of supine hypertension were recorded according to our previously published protocol [13]. DaTscan and brain MRI were also performed. The analysis of the DaTscan was qualitative and not quantitative. All images were reviewed by the same nuclear medicine consultant. Supine hypertension was defined as supine SBP > 140 mmHg or supine DBP > 90 mmHg [14]. Given the small sample size, summary

TABLE 1 Clinical features and investigation results in PAF patients with DaTscan positive.

Patient; sex/age at symptom onset (years)	Age at autonomic assessment (years)/DD at last review (years)	Clinical features						
		CV-OIS	ED	LUTS	CNS feature	DD at DaTscan (years) and indication	DaTscan findings	Other investigations
1; male / 42	45/7	First presenting symptom	Yes	UF, UU, ISC required	No	7 / Severe bladder dysfunction; mild tremor (reviewed by MD specialist)	Severe reduction of tracer uptake in the putamen bilaterally with relatively preserved activity within the caudate nuclei	Brain MRI: normal Uroflow: hypo-contractile detrusor
2; male / 63	68/7	OIS developed later in the course of disease	Yes	UF, UU	No	6 / Subtle oculomotor features (breakup of lateral saccades with no other cerebellar features)	Subtle reduction of tracer uptake in the left putamen	Brain MRI: mild generalized volume loss with normal basal ganglia Cardiac MIBG: markedly reduced cardiac I-123 MIBG uptake
3; male / 48	53/8	OIS developed later in the course of the disease	Yes	UF, UU, ISC and then suprapubic catheter required	RBD	6 / Mild tremor and severe bladder dysfunction	Reduced tracer uptake in the right striatum	Brain MRI: normal Urodynamics: signs of detrusor acontractility Anal sphincter EMG: abnormal study with numerous motor unit potentials which were abnormally prolonged bilaterally Cardiac MIBG: normal
4; male / 59	61/6	OIS developed later in the course of the disease	Yes	UF, UU, occasional urinary incontinence	RBD	6 / Mild tremor and severe bladder dysfunction (reviewed by MD specialist)	Markedly reduced tracer uptake in both striata. Changes are more profound in the putamen compared to the caudate and slightly more in the left striata compared to the right	2 brain MRIs, 4 years apart, showed progressive generalized volume loss with mild background of small vessel disease Cardiac MIBG: markedly reduced uptake in the myocardium consistent with autonomic dysfunction
5; male / 59	62 /4	First presenting symptom	Yes	UU, occasional urinary incontinence. Increased PVR	Anosmia/ RBD	4 / Abnormal MRI brain and severe bladder dysfunction	Reduced tracer uptake within the striatum (mostly putamen) bilaterally	Brain MRI: mild midbrain atrophy not suggestive for MSA or PSP Cardiac MIBG: very poor uptake of tracer in the myocardium

Abbreviations: CNS, central nervous system; CV, cardiovascular; DaTscan, dopamine transporter imaging; DD, disease duration; ED, erectile dysfunction; EMG, electromyogram; ISC, intermittent self-catheterization; LUTS, lower urinary tract symptoms; MD, movement disorder; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; MSA, multiple system atrophy; OIS, orthostatic intolerance symptoms; PAF, pure autonomic failure; PSP, progressive supranuclear palsy; PVR, post void residual; RBD, rapid eye movement sleep behaviour disorder; UF, urinary frequency; UU, urinary urgency.

TABLE 2 Clinical features and investigation results in PAF patients with DaTscan negative.

Patient; sex/age at symptom onset (years)	Age at autonomic assessment (years)/DD at last review (years)	Clinical features			CNS features	DD at DaTscan (years) and indication	DaTscan findings	Other investigations
		CV-OIS	ED	LUTS				
6; male / 51	57/17	First presenting symptom	Developed later in the course of the disease	Nocturia and urinary urgency	No	15/ Bladder dysfunction with significant increased PVR and need for catheterization	Normal availability of presynaptic dopamine transporters	Brain MRI: not performed due to cardiac pacemaker Nerve conduction study: absent sympathetic skin response
7; female / 44	54/15	First presenting symptom	NA	No in the early stage. Later in the disease course she developed severe urinary urgency and recurrent UTI	RBD	15/ Bladder dysfunction	Normal availability of presynaptic dopamine transporters	Brain MRI: normal Nerve conduction study: absent sympathetic skin response from the right foot and no evidence for large fibre neuropathy
8; female / 47	49/13	First presenting symptom	NA	Urinary urgency, frequency and incomplete bladder emptying	RBD	12/ Severe bladder dysfunction	Normal availability of presynaptic dopamine transporters	Brain MRI: normal Nerve conduction study: absent sympathetic skin response
9; female / 48	58/13	First presenting symptom	NA	Urinary urgency, frequency, incomplete bladder emptying and voiding difficulty, ISC not required	No	10/ Abnormal MRI brain, subtle ataxia (was reviewed by MD specialist), abnormal sphincter EMG	Normal availability of presynaptic dopamine transporters	Brain MRI: pontocerebellar volume loss Anal sphincter EMG study: evidence for chronic denervation Cardiac MIBG: no uptake of MIBG in the myocardium Nerve conduction study: absent sympathetic skin response
10; male / 64	66/3	First presenting symptom	No	Urinary frequency and urgency and increased PVR	RBD and anosmia	2/ Early severe bladder dysfunction	Normal availability of presynaptic dopamine transporters	Brain MRI: chronic microvessel disease changes Cardiac MIBG: reduced uptake of MIBG in the myocardium

Abbreviations: CNS, central nervous system; CV, cardiovascular; DaTscan, dopamine transporter imaging; DD, disease duration; ED, erectile dysfunction; EMG, electromyogram; ISC, intermittent self-catheterization; LUTS, lower urinary tract symptoms; MD, movement disorder; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; NA, not applicable; OIS, orthostatic intolerance symptoms; PAF, pure autonomic failure; PVR, post void residual; RBD, rapid eye movement sleep behaviour disorder; UTI, urinary tract infection.

TABLE 3 Patients' demographics and disease duration in both DaTscan positive and DaTscan negative groups.

	Patients $n=10$		DaTscan positive $n=5$		DaTscan negative $n=5$		
	Median	Inter quartile range (IQR)	Median	IQR	Median	IQR	*p* value
Age of symptom onset (years)	49.5	12	59	16	48	12	0.37
Age at autonomic assessment (years)	57.5	9	61	16	57	10.5	0.41
Disease duration at last clinical assessment (years)	7.5	7	7	2.5	13	8	0.07
Disease duration at DaTscan (years)	6.5	6	6	1.5	12	9	0.07

statistics were presented as the median and interquartile range (IQR). Mann–Whitney non-parametric statistical analysis was used to compare groups.

Standard protocol approvals, registrations and patient consents

The brain donor programme and protocols were approved by the NRES Committee London-Central (16/LO/1656) IRAS number 197553. Written informed consent was obtained from all the patients.

RESULTS

Seventy patients were evaluated at the Autonomic Unit between 2015 and 2021 for suspected PAF. Ten patients (seven male and three female) exhibited atypical features, as outlined in Methods and described in Tables 1 and 2, and were included in this retrospective study.

Patients had a median age of 49.5 years (IQR 12 years) at disease onset (as age at first autonomic symptoms). The median age during the first assessment at our autonomic centre was 57.5 years (IQR 9 years). The median disease duration was 7.5 years (IQR 7 years) at the last clinical appointment (Table 3).

All patients underwent autonomic function tests, an imaging study and a neurological examination. PAF was diagnosed according to the criteria defined above. None of the 10 patients demonstrated neurological features meeting the international criteria for PD [15], DLB [16] or MSA [17] at their most recent follow-up (median duration of 7.5 years from disease onset). All the patients presented with orthostatic intolerance and other symptoms in keeping with autonomic dysfunction (Tables 1 and 2).

Autonomic function testing and investigation findings

All patients presented neurogenic OH on standing and on tilt table testing, an abnormal HR variability to deep breathing and abnormal BP and HR responses to the Valsalva manoeuvre, consistent with widespread parasympathetic and sympathetic failure (Table 4).

Five patients had abnormal (positive) DaTscans and five had normal DaTscans (referred to as a negative scan). Patients with positive DaTscans were all men and had more severe OH and urinary symptoms. Of those with a negative DaTscan, three were women.

Patients with a positive DaTscan were older at symptom onset compared to patients with a negative DaTscan (median age 59 vs. 48 years). They also had a shorter disease duration at the last clinical appointment (median 7 vs. 13 years) and at the time of the DaTscan (median 6 vs. 12 years).

Compared to the DaTscan negative group, patients with positive DaTscans had higher OIR (19.25, IQR 25.95, vs. 9.3, IQR 12.59), a greater fall in BP on standing (median ΔSBP 84 vs. 66.75 mmHg; median ΔDBP 50 vs. 31 mmHg) and a greater rise in HR on standing (median of 6/min vs. 2/min) although the results did not reach statistical significance.

The frequency of RBD was similar in both groups (3/5).

Cardiac MIBG was performed in six patients; it showed evidence for sympathetic denervation in two with a negative DaTscan and in three with a positive DaTscan. DaTscan, brain MRI and cardiac MIBG are displayed in Figures 1–3 respectively.

REPRESENTATIVE CASES

Case 1

A middle-aged man presented with a 6-year history of prominent genitourinary dysfunction (erectile dysfunction, urinary urgency, frequency and retention requiring catheterization), and a 5-year history of orthostatic intolerance, syncope, anhidrosis, dry eyes and RBD. Neurological examination was unremarkable except for intermittent postural tremor. Autonomic testing showed significant neurogenic OH, abnormal BP response to the Valsalva manoeuvre and absent respiratory sinus arrhythmia. Catecholamine (both noradrenaline [NA] and adrenaline [A]) levels were at the lower normal limits (201 pg/mL and 15 pg/mL for NA and A, respectively). Normal ranges are 200–500 pg/mL for NA and 20–150 pg/mL for A with minimal rise on tilt (215 pg/mL and 16 pg/mL for NA and A, respectively). Brain MRI was normal. A urodynamic study revealed detrusor non-contractility. Anal sphincter electromyogram (EMG) was abnormal with numerous prolonged motor unit potentials bilaterally consistent

TABLE 4 Detailed cardiovascular autonomic function test results in both groups.

Patient number	Medication on test	HUT				Standing			Valsalva ratio	RSA	Noradrenaline (pg/mL) (normal 200–500 pg/mL)	Adrenaline (pg/mL) (normal 20–150 pg/mL)	24-h circadian rhythm	Supine HTN
		ΔSBP	ΔDBP	ΔHR	Tilt time OIR	ΔSBP	ΔDBP	ΔHR						
1	None	61	45	2	2 30.5	101.5	66	0	1.03	Absent	109/NA	NA	Abnormal	No
2	Fludro and Mido	74.5	47	22	2 37.25	96	49.5	12	1.28	Absent	206/218	16/19	Not available	Yes
3	None	64.5	31.5	7.5	10 6.45	68	33	5	1.1	Minimal	201/215	15/16	Reversed	Yes
4	Fludro	77	47.5	21	4 19.25	84	50	17	1.1	Absent	191/199	41/58	Reversed	No
5	Fludro and Mido	94	45	13	10 9.4	83	52	6	1.01	Absent	162/165	19/20	Reversed	No
6	Fludro	82	29	−1	9 9.11	105	54	−8	1.1	Minimal	217/NA	25/NA	Reversed	Yes
7	None	73	32	−4	5 14.6	53	31	−4	1.05	Absent	216/213	21/20	Preserved	No
8	Fludro	98	46.5	17	4 24.5	65 (sitting)	22	2	1.02	Absent	160/172	NA	Reversed	Yes
9	Mido	93	52.5	26	10 9.3	80.5	50	28	1.01	Absent	203/236	15/18	Reversed	Yes
10	None	48	24	14	10 4.8	39	17	3	1.32	Inadequate	191/189	19/20	Preserved	Yes

Abbreviations: ΔDBP, change in diastolic blood pressure; ΔHR, change in heart rate; ΔSBP, systolic blood pressure; Fludro, fludrocortisone; HTN, hypertension; HUT, head-up tilt; Mido, midodrine; NA, not applicable; OIR, orthostatic intolerance ratio (ΔSBP on head-up tilt/minutes of tilt tolerance); RSA, respiratory sinus arrhythmia.

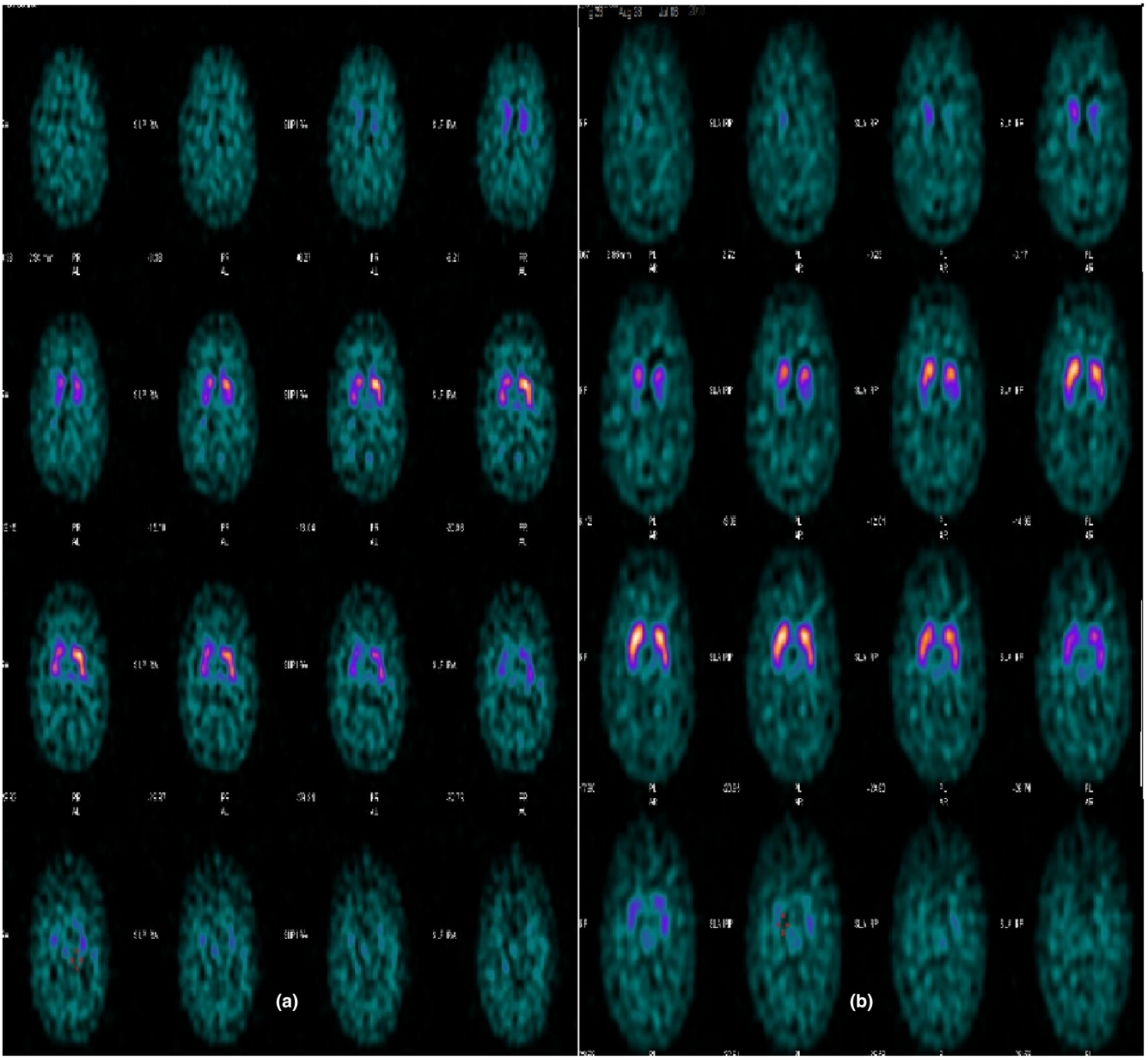

FIGURE 1 DaTscan for patients 3 (a) and 7 (b) showing reduced presynaptic availability of dopamine transporter in patient 3 (a) and preserved availability in patient 7 (b).

with an involvement of Onuf's nucleus. A DaTscan showed reduced availability of the presynaptic DAT in the right striatum, compatible with nigrostriatal dopaminergic degeneration.

The patient had been regularly followed up in our clinic. He had an 8-year history of widespread autonomic failure and RBD with no neurological features suggestive of widespread α-synucleinopathy (no parkinsonism, cognitive impairment or cerebellar features) at last clinical assessment.

Case 2

A middle-aged woman presented with a 7-year history of progressive orthostatic intolerance, syncopal episodes, constipation, heat intolerance and a 3-year history of incomplete bladder emptying. Neurological examination showed minor difficulties in tandem gait but no gait ataxia or other cerebellar signs. Baseline autonomic testing showed OH, abnormal BP and HR responses to the Valsalva manoeuvre, absent HR variability in deep breathing, and borderline low catecholamine levels (203 and 15 pg/mL for NA and A, respectively) with minimal rise on tilt (236 and 18 pg/mL for NA and A, respectively).

Brain MRI showed subtle pontocerebellar atrophy with mild progression after 2 years, although cerebellar features were not observed at last follow-up (Figure 2). Cardiac MIBG showed no myocardial uptake, and DaTscan was normal. Anal sphincter EMG showed some chronic denervation changes consistent with involvement of Onuf's nucleus. The patient was started on midodrine and

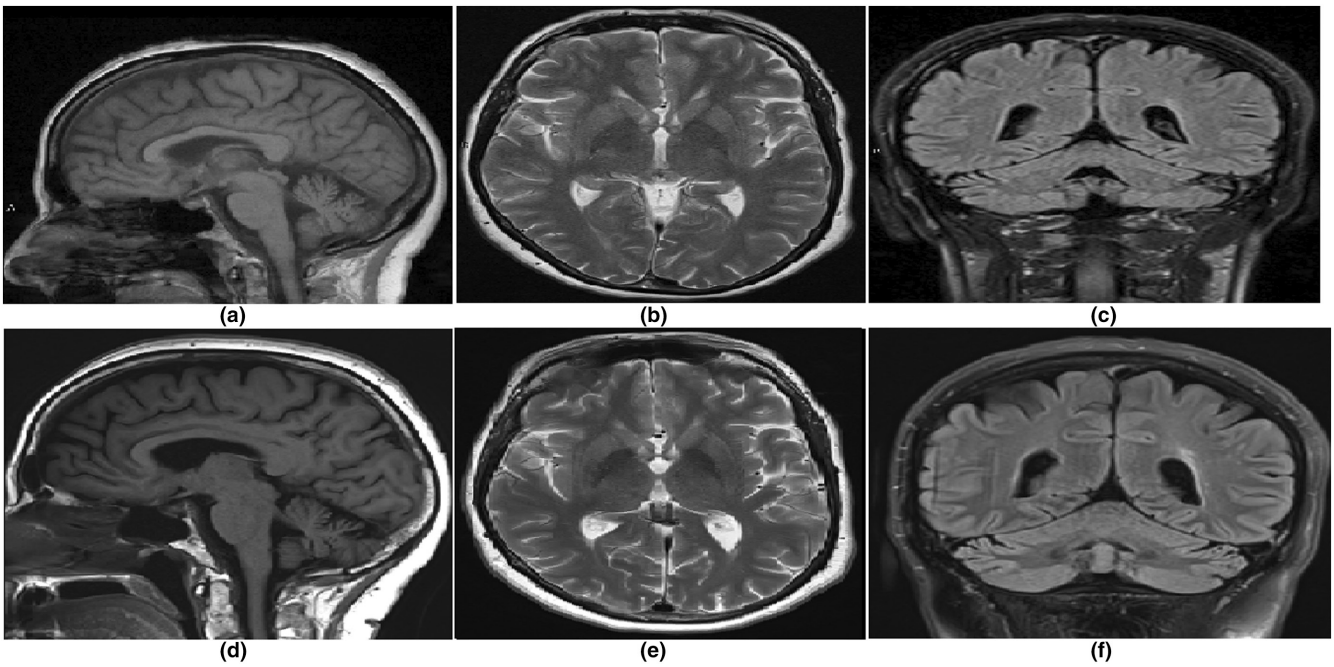

FIGURE 2 Brain MRI of patient 9: (a), (b), (c) in 2018 and (d), (e), (f) in 2020, showing mild pontocerebellar atrophy with subtle progression.

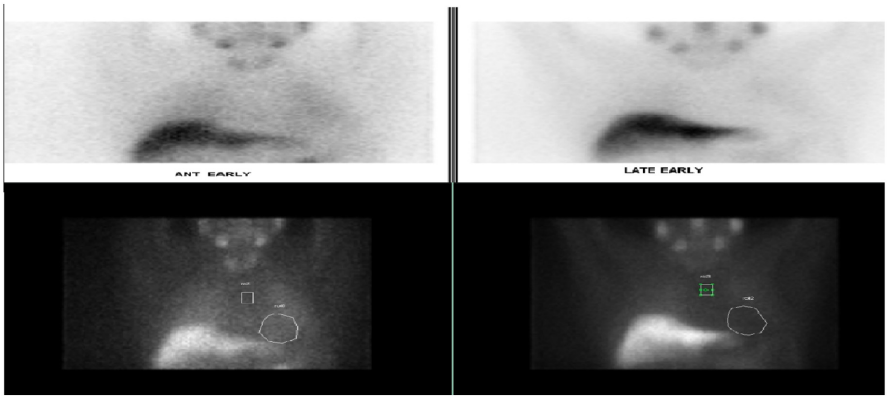

FIGURE 3 Shows very poor uptake of tracer in the myocardium in patient number 5.

fludrocortisone with some improvement in orthostatic intolerance. Despite mild pontocerebellar atrophy with abnormal sphincter EMG, the patient did not meet the criteria for MSA, as cerebellar dysfunction was not evident 13 years after onset. However, it still cannot be excluded that the patient might represent a case of prodromal MSA which will develop later in the disease course as observed in previous cases in the literature [18].

Neither patient had motor symptoms to meet the criteria for phenoconversion to a widespread α-synucleinopathy (MSA, PD or DLB); however, subtle motor signs such as mild bradykinesia, hypomimia or decreased amplitude of rapid alternating movements have been previously reported to be a risk factor for phenoconversion [4, 7].

DISCUSSION

A subgroup of patients with longstanding PAF had evidence of central involvement as indicated by subtle neurological signs and degeneration of the nigrostriatal dopaminergic neurons on DaTscan. In our cohort of patients evaluated for suspected PAF, 10/70 (14,2%) patients presented with atypical features which warranted further investigation with DaTscan. Amongst patients with atypical features, 50% of PAF patients had abnormal DaTscan. Patients with a positive DaTscan were all men, older at symptom onset, had shorter disease duration at presentation and had prominent urinary symptoms (storage and voiding).

The shorter disease duration and greater OIR may point towards a more severe disease course. Patients with positive DaTscans also tended to have a greater HR rise on standing which has previously been reported in patients with PAF who were later diagnosed with MSA [4, 7].

Markedly reduced availability of the presynaptic dopaminergic transporter reflects a central involvement with nigrostriatal degeneration. REM sleep behaviour can also be indicative of this central involvement [1, 7]. The frequency of REM sleep behaviour and anosmia was similar in both groups. However, the presence of REM sleep behaviour was only obtained from history and none of our subjects had a formal sleep study.

In one paper, 43 patients with an isolated REM sleep behaviour underwent DaTscan and were followed up for 2.5 years. Eight out of 27 participants with abnormal DaTscans developed full-blown PD, MSA or LBD after 2.5 years, whereas all 19 patients with normal DaTscans remained disease-free during the follow-up period [19]. This observation suggests that DaTscans may be a useful biomarker for early subclinical nigrostriatal dysfunction in patients with α-synucleinopathy without clear motor symptoms [20].

Pure autonomic failure with an abnormal DaTscan has been described in a 72-year-old woman who was followed up for 11 years. That patient had no signs of parkinsonism or cognitive symptoms at follow-up despite the abnormal DaTscan [10]. However, DaTscan abnormality can predate the clinical onset of PD by many years. Müller et al. previously described abnormal DaTscans in patients up to 5 years before clinical manifestation of PD [21]. Our patients with a reduction in presynaptic DAT availability and no concurrent motor symptoms or signs were followed up to a maximum of 2 years after their DaTscans. A longer follow-up might confirm whether the patients will retain their PAF phenotype or develop more widespread neurological features.

Previous postmortem studies on PAF with no clinical signs of conversion to PD or MSA found evidence of central Lewy body aggregations suggesting that some degree of central involvement might be an inherent part of PAF pathology [22]. Central nervous system involvement cannot be excluded as part of the PAF pathophysiology, and it remains uncertain whether phenoconversion to a more widespread α-synucleinopathy may occur in those with an abnormal DaTscan. The former may be supported by patients in our cohort with longstanding PAF (8 years from symptom onset) and abnormal DaTscan without extra-pyramidal features. Moreover, an abnormal DaTscan with isolated hyposmia or REM sleep behaviour has previously been described without phenoconversion even after a few years of follow-up [23].

Patients included in our study had only one DaTscan in their clinical course after a median disease duration of 12 years in the DaTscan negative group compared to 6 years in the DaTscan positive group. Therefore, it is not clear at which time point the DaTscan turned positive in the DaTscan positive group.

The central nervous system involvement might correlate with the severity of autonomic symptoms. Predominant caudate nucleus affection can be associated with the severity of the gastrointestinal, cardiovascular and lower urinary symptoms in patients with PD [24–26]. However, the putamen nucleus was more severely affected in our patients. It was also suggested that the severity of DAT tracer uptake reduction might correlate with the severity of lower urinary symptoms in patients with PD [26]. Whether this central nervous system involvement in PAF patients leads to more prominent genitourinary dysfunction is unknown. Although genitourinary symptoms were reported in both groups, patients in the abnormal DaTscan group had pronounced genitourinary dysfunction, erectile dysfunction and bladder symptoms requiring intermittent catheterization in some patients. One patient with an abnormal anal sphincter EMG also required a suprapubic catheter. This can also herald the phenoconversion to MSA.

A strong correlation was also found between constipation in early PD patients and the reduced striatal DAT availability (especially the caudate binding ratio) suggesting that a nigrostriatal pathology might play a role in gastrointestinal dysfunction [24]. The reduction in DAT availability, especially in the caudate nucleus, was previously reported to be associated with the severity of autonomic symptoms, namely cardiovascular and gastrointestinal symptoms in patients with PD [24]. In our cohort, however, no difference in gastrointestinal symptom severity was noticed between these two groups.

Further research is needed in future to ascertain which biomarkers predict conversion of isolated autonomic failure to widespread α-synucleinopathy. The new α-synuclein seed amplification assay is a potential biomarker if it proves to be both a sensitive and specific test [27, 28]. The main limitation of the study is the small sample size, lack of formal sleep studies and the absence of a follow-up DaTscan in our patients. Further monitoring is planned to address these shortcomings and to evaluate a prospective cohort of PAF patients.

The strength of this paper is the long follow-up period with a minimum of 4 years disease duration in the DaTscan positive group. To the best of our knowledge, this is one of the earlier papers to describe the degeneration of the nigrostriatal dopaminergic neurons using DaTscan imaging in a series of systematically evaluated PAF patients without clinical features indicative of PD, MSA or DLB.

CONCLUSION

The reduced availability of the presynaptic dopaminergic transporter using DaTscan may be a useful biomarker to identify central nervous system involvement in patients with autonomic failure and no clinical evidence of central nervous system dysfunction who have an initial diagnosis of PAF.

AUTHOR CONTRIBUTIONS

Rana Alnasser Alsukhni: Conceptualization; methodology; software; data curation; investigation; writing – review and editing; writing – original draft; formal analysis. **Ekawat Vichayanrat:** Writing – original draft; writing – review and editing; supervision; formal analysis. **Shiwen Koay:** Writing – review and editing. **Laura May Davis:** Writing – review and editing; data curation; software; resources. **Gordon Ingle:** Supervision; writing – review and editing. **Patricia McNamara:** Supervision; writing – review and editing. **Jalesh N. Panicker:** Supervision; writing – review and editing; validation. **Kailash P. Bhatia:** Supervision; validation; writing – review and editing. **Christopher Mathias:** Writing – review and editing; supervision. **Jamshed Bomanji:** Writing – review and editing; supervision. **Valeria Iodice:** Conceptualization; writing – review and editing; supervision; validation; project administration.

CONFLICT OF INTEREST STATEMENT

All authors declare they have no competing interests.

DATA AVAILABILITY STATEMENT

Due to the sensitive nature of the data collected for this study, anonymized data pertaining to the research presented will be made available upon reasonable request from external qualified investigators.

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How to cite this article: Alnasser Alsukhni R, Vichayanrat E, Koay S, et al. Abnormal dopamine transporter imaging in pure autonomic failure: a potential biomarker of central nervous system involvement. *Eur J Neurol*. 2023;00:1-10. doi:10.1111/ene.16169