Urinary dysfunction is associated with higher disease burden in patients with Parkinson's disease

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OBJECTIVE

To explore the association between levels of α-synuclein burden and urinary dysfunction in early *de novo* Parkinson's disease (PD) patients.

BACKGROUND

Urinary dysfunction is one of the most common non-motor symptom of PD, often unresponsive to dopaminergic treatment and associated with poorer quality of life [1]. Urinary dysfunction often precedes motor symptoms and has been associated with a faster disease progression [2]. Autonomic nervous system plays a pivotal role in the control of bladder function and a lesion or neurodegeneration of brainstem can cause bladder overactivity and subsequently urinary urgency, increased frequency and incontinence.

PD patients with urinary dysfunction showed lower dopamine transporter (DAT) single positron emission tomography (SPECT) binding than PD without urinary dysfunction [3]. *Post-mortem* studies have shown the concomitant occurrence of dopaminergic damage and deposition of α-synuclein in the autonomic nervous system and in the lateral collateral pathway, a region of the sacral spinal dorsal horn important for the relay of pelvic visceral afferents. Deposition of α-synuclein in this region may contribute to the development of urinary dysfunction. However, the relationship between urinary dysfunction and α-synuclein pathology has not been explored.

Table 1 Demographic and motor symptoms of PD with and without urinary dysfunction

	PD with urinary dysfunction (n=205)	PD without urinary dysfunction (n=193)
Age at screening, mean ±SD	63.3 ± 9.4	59.9 ± 9.7*
Gender male, % (n)	63.9% (131)	66.8% (129)
PD duration (months), mean ±SD	6.9 ± 6.8	6.0 ± 5.8
Hoehn and Yahr stage, mean ± SD	1.6 ± 0.5	1.5 ± 0.5*
Motor Subtypes, % (n)	AR: 62.0% (127) Mixed: 12.2% (25) TD: 25.9% (53)	AR: 59.1% (114) Mixed: 8.3% (16) TD: 32.6% (63)
MDS-UPDRS Part-I, mean ± SD	1.4 ± 1.8	1.0 ± 1.3*
MDS-UPDRS Part-I Quest, mean ± SD	5.7 ± 3.3	2.9 ± 2.3*
MDS-UPDRS Part-II Quest, mean ± SD	7.2 ± 4.5	4.5 ± 3.4*
MDS-UPDRS Part-III, mean ± SD	21.6 ± 8.4	18.8 ± 8.6*
MDS-UPDRS Total, mean ± SD	35.9 ± 13.1	27.3 ± 11.2*
Bradykinesia subscore, mean ± SD	10.6 ± 5.2	9.5 ± 5.6*
Postural instability subscore, mean ± SD	4.0 ± 2.7	3.5 ± 2.5*
Rigidity subscore, mean ± SD	1.0 ± 1.0	0.6 ± 0.8*
Resting Tremor Amplitude subscore, mean ± SD	1.5 ± 1.3	1.5 ± 1.4
Resting Tremor Constancy subscore, mean ± SD	1.3 ± 1.2	1.4 ± 1.2

*P values <0.05; P values >0.1. (*t*-test and Mann-Whitney U tests, Bonferroni corrected).

METHODS

In this study we have extracted and analysed data of 398 early *de novo* PD patients using the Parkinson's Progression Markers Initiative database. Data of PD patients were compared to those from a group of age/gender matched healthy controls (HCs). Urinary dysfunction has been evaluated using MDS-UPDRS Part-I item 1.10 and correlated with CSF α-synuclein, striatal [^{123}I]FP-CIT bindings and clinical scales.

RESULTS (1/2)

The prevalence of urinary dysfunction was 51.5% (205/398) in the early *de novo* PD patients, and was higher compared to a group of age- and gender-matched healthy controls (24.3%; 46/189; *P*<0.0001). Compared to PD patients without urinary dysfunction, PD patients with urinary dysfunction had a higher burden of non-motor symptoms including worse autonomic dysfunction (*P*<0.001), depression (*P*=0.008), REM behavioural disorders (*P*=0.048), disability (ADL) (*P*=0.016), sleep problems (*P*=0.011), daytime sleepiness (*P*<0.001), constipation (*P*<0.001) and fatigue (*P*<0.001). No other differences were found between PD patients with and without urinary dysfunction. Compared with PD without urinary dysfunction, PD patients with urinary dysfunction had lower putamen (*P* <0.0001), caudate (*P* <0.0001), and total striatum (*P* <0.0001) [^{123}I]FP-CIT uptake values.

RESULTS (2/2)

Urinary dysfunction in PD patients was associated with older age (r=0.224, *p*<0.001), and therefore we used age as a covariate. Higher urinary dysfunction correlated with higher CSF α-synuclein (r=0.161, *p*=0.035) levels and with lower putamen (r=-0.247, *p*<0.001), caudate (r=-0.224, *p*<0.001) and total striatum (r=-0.247, *p*<0.001) [^{123}I]FP-CIT uptake values (Figure 1). Higher urinary dysfunction in PD patients correlated with higher MDS-UPDRS total score (r=0.378, *p*<0.001), higher MDS-UPDRS Part-I Quest (r=0.560, *p*<0.001), higher MDS-UPDRS Part-II Quest (r=0.341, *p*<0.001),), higher MDS-UPDRS Part-III (r=0.161, *p*=0.001) increased postural instability (r=0.241, *p*=0.012), higher autonomic dysfunction scores (r=0.558, *p*<0.0001), higher Epworth Sleeping Scale score (r=0.207, *p*=0.016), higher REM sleep behaviour disorder score (r=0.221, *p*=0.008), increased sleep problems (r=0.293, *p*<0.001), increased daytime sleepiness (r=0.241, *p*<0.001), higher constipation scores (r=0.247, *p*<0.001) and increased fatigue (r=0.251, *p*<0.001).

No other correlations were found.

Figure 1 Correlations between urinary dysfunction, CSF α-synuclein and [^{123}I]FP-CIT striatal bindings

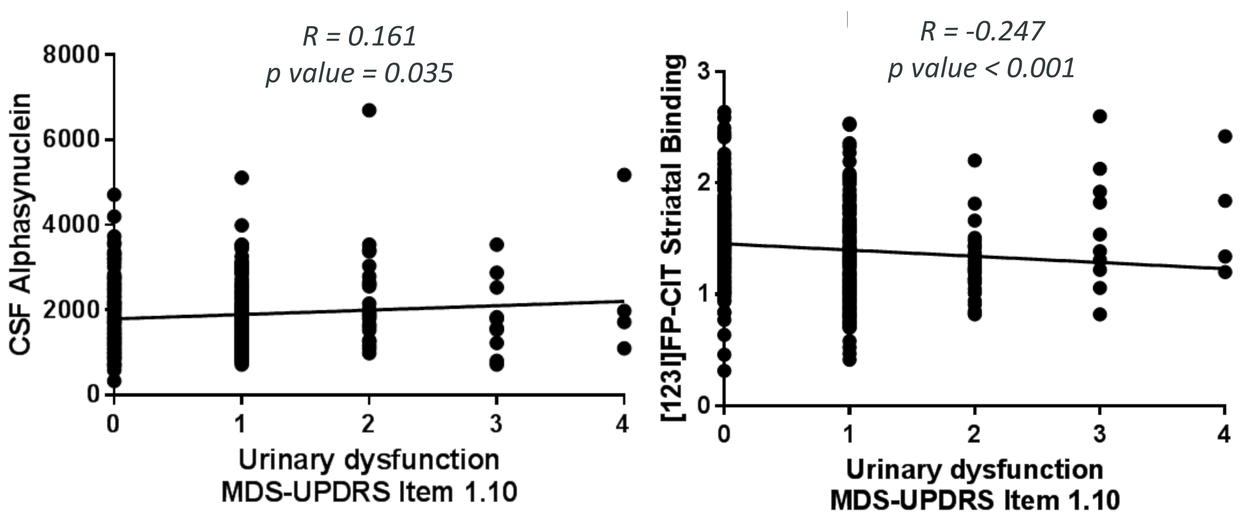
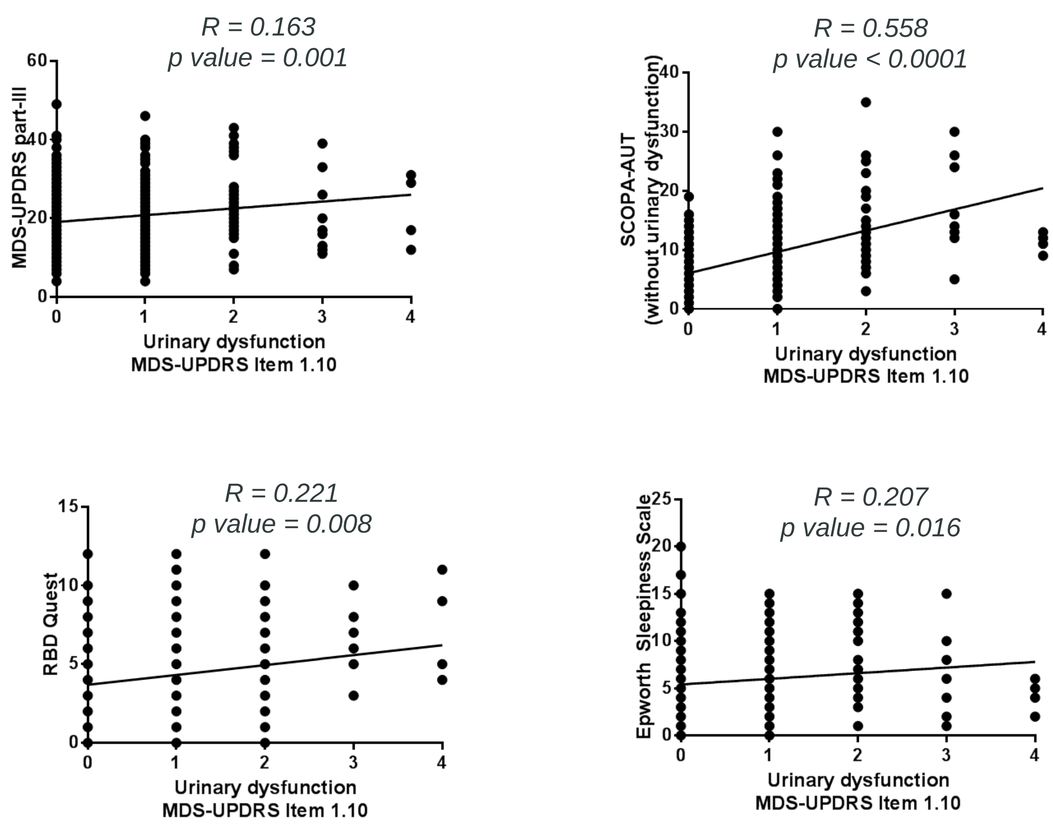


Figure 2 Correlations between urinary dysfunction and clinical scales



CONCLUSION

Urinary dysfunction could be a marker of overall higher motor and non-motor burden in patients with PD, and is associated with higher dopaminergic deficits and CSF pathology. The identification of urinary dysfunction at the time of PD diagnosis may be cardinal in the management of PD patients, and will aid in the screening of patients with faster disease progression that might be get benefit from clinical trials.

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