Constipation in early *de novo* Parkinson's disease: Prevalence and correlates with clinical features, imaging and non-imaging biomarkers

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OBJECTIVE

To explore the association between constipation and clinical features, imaging and non-imaging biomarkers in early *de novo* (untreated) Parkinson's disease (PD) patients.

BACKGROUND

Constipation is a common and bothersome non-motor symptom of PD, often poorly identified and inadequately treated [1]. Similarly to other non-motor symptoms in PD, non-dopaminergic pathways could be implicated in the development of constipation in PD [2]. *Post-mortem* studies have shown that deposition of α-synuclein inclusions in the gut occur early in the course of PD. An abnormal α-synuclein agglomeration that spread from the gut to the substantia nigra *via* vagus nerve has been suggested as *primum movens* of PD [3]. Constipation has been suggested to precede the development of motor symptoms in PD by a decade. However is unclear whether the development of constipation in PD is associated with other symptoms or with markers of motor pathology such as the dopaminergic degeneration in the striatum [4].

Table 1 Demographic and motor symptoms of PD with and without constipation

	PD with constipation (n=132)	PD without constipation (n=266)
Age at screening, mean ±SD	64.6 ± 9.3	60.2 ± 9.6*
Gender male, % (n)	60.6 (80)	67.7 (180)
PD duration (months), mean ±SD	6.0 ± 5.7	6.7 ± 6.7
Hoehn and Yahr stage, mean ± SD	1.6 ± 0.5	1.5 ± 0.5
Motor Subtypes, % (n)	AR: 60.6% (80) Mixed: 10.6% (14) TD: 28.8% (38)	AR: 60.5% (161) Mixed: 10.2% (27) TD: 29.3% (78)
MDS-UPDRS Part-I, mean ± SD	15.98 ± 2.39	16.21 ± 3.19*
MDS-UPDRS Part-I Quest, mean ± SD	1.6 ± 1.6	1 ± 1.5*
MDS-UPDRS Part-II Quest, mean ± SD	6.3 ± 3.4	3.4 ± 2.6*
MDS-UPDRS Part-III, mean ± SD	7.2 ± 4.4	5.3 ± 4.0
MDS-UPDRS Total, mean ± SD	36.8 ± 12.6	29.2 ± 12.4*
Bradykinesia subscore, mean ± SD	21.7 ± 8.1	19.5 ± 8.8
Postural instability subscore, mean ± SD	36.8 ± 12.6	29.2 ± 12.4*
Rigidity subscore, mean ± SD	10.8 ± 5.2	9.8 ± 5.6
Resting Tremor Amplitude subscore, mean ± SD	1.0 ± 1.0	0.7 ± 0.9
Resting Tremor Constancy subscore, mean ± SD	3.9 ± 2.7	3.7 ± 2.6

*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 using the Parkinson's Progression Markers Initiative database for investigating the role of constipation in early *de novo* PD patients. Data of PD patients were compared to those from a group of age/gender matched healthy controls (HCs). Constipation has been evaluated using MDS-UPDRS Part-I item 1.11 and correlated with clinical features, molecular imaging ([^{123}I]FP-CIT SPECT) and non-imaging (CSF α-synuclein, total tau, ptau-$_{181}$ and Abeta$_{1-42}$) biomarkers.

RESULTS

The prevalence of constipation was 33.2% (132/398) in the early *de novo* PD patients, and was higher compared to a group of age- and gender-matched healthy controls (12.7%; 24/189; p<0.0001).

[^{123}I]FP-CIT SPECT imaging and Cerebrospinal fluid (CSF) and serum data

No differences were found in caudate (p>0.10), putamen (p>0.10), and total striatal (p>0.10) [^{123}I]FP-CIT uptake values between PD patients with and without constipation. CSF α-Syn, t-tau, p-tau$_{181}$, and Abeta$_{42}$, and serum IGF-1, urate and glucose were no different between PD patients with and without constipation.

Constipation in PD patients was associated with older age (r=0.728, p<0.001), and therefore we used age as a covariate. Higher constipation in PD patients correlated with higher MDS-UPDRS Total scores (r=0.285, p<0.001), higher MDS-UPDRS Part-I scores (r=0.454, p<0.001), higher higher MDS-UPDRS Part-II scores (r=0.217, p<0.001), increased postural instability (r=0.190, p=0.012), higher autonomic dysfunction scores (r=0.358, p<0.0001), higher depression scores (r=0.187, p=0.024), higher REM sleep behaviour disorder score (r=0.228, p<0.0001), increased daytime sleepiness (r=0.187, p=0.033), higher urinary dysfunction scores (r=0.232, p<0.0001), increased dizziness (r=0.214, p<0.0001) and increased fatigue (r=0.200, p=0.011). No other correlations were found.

Table 2 Non-motor symptoms in PD with and without constipation

	PD with constipation (n=132)	PD without constipation (n=266)
SCOPA-AUT°, mean ± SD	11.0 ± 5.9	7.2 ± 4.8*
GDS, mean ± SD	2.8 ± 2.6	2.1 ± 2.3*
Epworth Sleeping Scale, mean ± SD	6.4 ± 3.5	5.5 ± 3.4
RBDQ Score, mean ± SD	5.0 ± 2.9	3.7 ± 2.5*
STAI Total Score, mean ± SD	68.5 ± 18.9	63.9 ± 18.1
MoCA, mean ± SD	26.7 ± 2.6	27.3 ± 2.2
UPSIT, mean ± SD	20.9 ± 8.0	23.2 ± 8.3
ADL, mean ± SD	92.3 ± 5.9	93.7 ± 5.9
Cognitive impairment MDS-UPDRS Item 1.1, mean ± SD	0.4 ± 0.6	0.2 ± 0.5*
Hallucinations and Psychosis MDS-UPDRS Item 1.2, mean ± SD	0.1 ± 0.3	0.0 ± 0.1*
Depressed mood MDS-UPDRS Item 1.3, mean ± SD	0.4 ± 0.6	0.2 ± 0.5*
Anxious mood MDS-UPDRS Item 1.4, mean ± SD	0.5 ± 0.6	0.4 ± 0.6
Apathy MDS-UPDRS Item 1.5, mean ± SD	0.3 ± 0.5	0.2 ± 0.5
Sleep problems, MDS-UPDRS Item 1.7, mean ± SD	1.1 ± 1.1	0.8 ± 1.0
Daytime sleepiness, MDS-UPDRS Item 1.8, mean ± SD	0.9 ± 0.9	0.6 ± 0.7*
Pain and other sensations, MDS-UPDRS Item 1.9, mean ± SD	0.8 ± 0.9	0.7 ± 0.8
Urinary problems, MDS-UPDRS Item 1.10, mean ± SD	0.9 ± 0.9	0.6 ± 0.7*
Light headedness on standing, MDS-UPDRS Item 1.12, mean ± SD	0.5 ± 0.7	0.2 ± 0.5*
Fatigue, MDS-UPDRS Item 1.13, mean ± SD	0.8 ± 0.9	0.5 ± 0.7*

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

DISCUSSION

Our findings demonstrate a three-fold increased prevalence of constipation in early-untreated PD patients compared to age- and gender-matched healthy population, and suggest that constipation is a common and early feature of PD. Our data show that severity of constipation is associated with premotor symptoms of PD such as REM sleep behaviour disorder, autonomic dysfunction, dizziness and urinary dysfunction. Constipation was not associated with molecular markers of PD pathology including [^{123}I]FP-CIT SPECT, cerebrospinal fluid and serum markers. [^{123}I]FP-CIT SPECT assesses the integrity of dopamine transporters and is a marker of presynaptic dopaminergic terminal degeneration and a correlate of rigidity and bradykinesia in PD. Also, constipation in early-untreated PD was not associated with the severity of cardinal motor symptoms of PD such as rigidity, bradykinesia and tremor. These results provide evidence for a non-dopaminergic substrate underlying the development of constipation in PD.

CONCLUSION

Constipation is a common and early feature of Parkinson's disease, and is associated with premotor symptoms such as REM sleep behaviour disorder and autonomic dysfunction, which have been speculated to form the pre-motor stage of Parkinson's disease. The lack of association between constipation and motor markers of the disease such as the dopaminergic degeneration supports this hypothesis.

REFERENCES

1. Politis M, Wu K, Molloy S, P GB, Chaudhuri KR, Piccini P. Parkinson's disease symptoms: the patient's perspective. Mov Disord. 2010 25: 1646-1651.
2. Happe S, Baier PC, Helmschmied K, Meller J, Tatsch K, Paulus W. Association of daytime sleepiness with nigrostriatal dopaminergic degeneration in early Parkinson's disease. J Neurol 2007;254:1037-1043.
3. Braak H, Del Tredici K. Invited Article: nervous system pathology in sporadic Parkinson disease. Neurology 2008;70:1916e25.
4. Pagano G, Tan EE, Haider JM, Bautista A, Tagliati M. Constipation is reduced by beta-blockers and increased by dopaminergic medications in Parkinson's disease. Parkinsonism Relat Disord. 2015;21(2):120-5