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Constipation is reduced by beta-blockers and increased by dopaminergic medications in Parkinson's disease

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ABSTRACT

Background: Constipation is one of most frequent non-motor symptoms of Parkinson's disease (PD) and it may precede the clinical diagnosis of PD by years, with negative effects on quality of life. In contrast to motor features, levodopa is ineffective and possibly detrimental on constipation. Treatment of constipation in PD is non-specific and frequently unsuccessful. Stemming from a clinical observation of unexpected relief of bothersome constipation, abdominal bloating and pain after treatment with the beta-blocker carvedilol in one patient, we have evaluated the association between the use of beta-blockers and the presence of constipation in a large, unselected PD cohort.

Methods: Retrospective review of the medical records of every patient with a diagnosis of PD seen in the Movement Disorders clinic at Cedars-Sinai Medical Center from October 2010 to April 2014.

Results: 341 medical records with a primary diagnosis of PD were reviewed, 336 of which contained information about constipation. Overall, 205/336 patients (61%) reported constipation. Among the 66 subjects treated with beta-blockers at the time of the encounter of record, only 28 (42.4%) reported constipation. By comparison, among the 270 subjects not treated with beta-blockers, 177 (65.5%) had constipation (χ^2 test p value = 0.001). Multivariate logistic analysis showed an odds ratio (OR) of 0.293 for beta-blockers (95% C.I. 0.161–0.535, $p = 0.0001$), 2.287 for levodopa (95% C.I. 1.271–4.117, $p = 0.006$) and 1.805 for dopamine agonists (95% C.I. 1.039–3.136, $p = 0.036$).

Conclusions: Beta-blockers are associated with a lower risk of constipation, while dopaminergic treatments appear to increase risk of constipation.

1. Introduction

Constipation is one of most frequent non-motor symptoms (NMS) of Parkinson's disease (PD) [1] and one of the most widely studied manifestations of autonomic nervous system impairment in PD [2]. The pathophysiological basis of constipation in PD is a decreased colonic transit time and/or disturbed anorectal evacuation, which clinically translates into decreased stool frequency (<3 times a week) and difficulty in stool expulsion [3]. While the nature and extent of autonomic involvement in PD is still poorly understood [4], post-mortem neuropathological and biochemical studies in PD patients showed the concomitant occurrence of nigrostriatal degeneration and α-synuclein agglomeration in enteric nervous system [5]. In accordance with Braak theory [6] and consistently with several clinical findings [7], the neuropathologic involvement of the autonomic nervous system is a crucial characteristic of the early stage of the disease. It is postulated that the PD pathogenetic process might actually start in the enteric nervous system [8] and spread from there via the vagus nerve to reach the central nervous system [9]. In fact, constipation often precedes the onset of motor symptoms by many years [10]. Moreover, constipation in PD patients has been correlated with duration and severity of the disease suggesting that its treatment may also have an impact on disease progression [11].

In contrast to motor features, levodopa is generally not very helpful in the treatment of constipation associated with PD, and other treatments are non-specific and frequently ineffective [3].

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Considering the lack of efficacious treatment [12] and its negative impact on quality of life [13], constipation represents one of the main unmet needs of PD patients [14] and a challenging field of clinical research. Stemming from a clinical observation of unexpected relief of bothersome constipation, abdominal bloating and pain after treatment with the beta-blocker carvedilol in a PD patient, we have conducted a retrospective analysis of a large cohort in order to evaluate the association between the use of beta-blockers and the presence of constipation in PD.

2. Methods

We conducted a retrospective, cross-sectional medical record analysis of 341 consecutive patients with a diagnosis of idiopathic PD seen in the Movement Disorders clinic at Cedars-Sinai Medical Center (CSMC) in Los Angeles from October 2010 to April 2014. Demographic and clinical data, including vitals, motor and NMS, dopaminergic medications, comorbidities and anti-hypertensive medications were collected at the initial consultation visit. The CSMC institutional review board approved the medical chart review. The study was written according to the STROBE guidelines for Observational Studies in Epidemiology [15].

The complete medical records of PD patients, all examined by one physician (MT) and stored in the medical records-linkage system of CSMC, were reviewed and abstracted independently by two authors (JH and AB), to ascertain the occurrence of constipation. Constipation was defined by the presence of at least 1 of 3 criteria: 1) a diagnosis of constipation in the medical records, or, in the absence of a formal diagnosis in the medical records, 2) the use of drugs to treat constipation or 3) patient report of infrequent bowel movements, subjective complaint of straining at stooling, incomplete evacuation or abdominal bloating. In addition, we abstracted data on the concomitant use of some potentially constipation-inducing drugs (anticholinergics, antidepressants, calcium channel blockers and diuretics).

To directly compare different medications at doses of equivalent efficacy, all dopaminomimetics were converted to a total levodopa equivalent daily dosage (LED). The following formula was derived from a systematic review of LED reporting in PD patients [16]: Total LED = regular levodopa dose × 1 + levodopa continuous release dose × 0.75 + pramipexole dose × 100 + ropinirole dose × 20 + rotigotine dose × 30 + selegilne oral dose × 10 + selegilne sublingual dose × 80 + rasagiline dose × 100 + amantadine dose × 1 + apomorphine dose × 10 + tolcapone × 0.5 or entacapone × 0.33. Finally, we noted the type of beta-blocker used and in particular whether it was cardio-selective or able to cross the blood–brain barrier (BBB).

2.1. Statistical analysis

Categorical variables were expressed as proportion and compared by use of χ^2 test with risk ratios and 95% confidence intervals quoted. Normally distributed, continuous variables were expressed as mean ± standard deviation and compared by the use of Student *t* test. Normality of data distribution was evaluated using the Kolmogorov-Smirnov test. The Pearson's correlation coefficient was calculated to assess the correlation between use of beta-blockers and presence of constipation. A separate sub-analysis compared the effects on constipation of cardio-selective versus non cardio-selective beta-blockers. Similarly, we compared the effects of beta-blockers crossing the BBB versus not crossing the BBB.

To determine the independent predictors of constipation, a logistic regression analysis was performed. Variables achieving $p < 0.1$ on univariate analysis were then included in a multivariate analysis. An additional logistic regression analysis including smoking consumption as confounding variable was performed because this factor is associated with impaired gastrointestinal function. In addition, further logistic regression analyses were conducted stratifying subjects by LED and by type and dose of beta-blocker. To assess the effects of dopaminergic treatments (levodopa or dopamine agonists) on constipation, a multivariable logistic regression analysis with a different degree of dopaminergic therapy (no therapy, levodopa alone, dopamine agonists alone, levodopa + dopamine agonists) was performed, including variables achieving $p < 0.1$ on univariate analysis and using no therapy as the reference group.

Association between constipation and other non-motor symptoms (NMS) was evaluated in univariate and multivariate logistic regression analysis including total and each NMS, separately. Total NMS score was defined as the sum of the presence of any of the following 16 symptoms: hyposmia, urgency, nocturia, drooling, hyperhydrosis, orthostatic hypotension (OH), dizziness, forgetfulness, attention deficit, apathy, anxiety, depression, REM behavior disorder, insomnia, fatigue and pain. A subscore of autonomic NMS was defined as the sum of 7 symptoms, including hyposmia, urgency, nocturia, drooling, hyperhydrosis, OH and dizziness.

Using heart rate (HR) as a surrogate marker of beta-blocker effectiveness, a sensitivity analyses was performed by subdividing study subjects into two groups according to HR: 1) above or equal to 80 beats per minute (bpm) or 2) below 80 bpm. Another sensitivity analysis was obtained using markers of disease severity, including the Unified Parkinson's Disease Rating Scale motor score (UPDRS III), either OFF or ON, and the NMS score (total and autonomic), in a multivariable logistic regression analysis with all other predictors of constipation achieving $p < 0.1$ on univariate analysis.

Odds ratios (OR) and 95% CIs were calculated for each multivariate analysis. All data were analyzed by SPSS software (version 20; SPSS, Chicago, IL) and STATA software (version 12.0; StataCorp, College Station, TX). Statistical significance was accepted at p value ≤ 0.05.

3. Results

3.1. Patient characteristics

Characteristics of the overall study population and of the patients with and without constipation are shown in Table 1. From the original study population of 341 patients, 5 patients were excluded because no information about constipation could be found in their medical records. Therefore, the final study population consisted of 336 PD patients, 217 of which were male (64.6%), with mean age of 68.46 ± 10.64 years and average PD duration of 7.46 ± 5.84 years. Two hundred thirty (68.5%) patients were treated with levodopa, of which 150 were on monotherapy. One hundred three patients (30.7%) were on dopamine agonists, of which 25 were on monotherapy. LED was on average 593.01 ± 560.20 mg/day. Among other antiparkinsonian medications, 103 patients (30.7%) were treated with a monoamino-oxidase inhibitor, 37 (11%) were taking amantadine and 27 (8%) were on an anticholinergic medication (Table 1). Other treatments included 71 patients (21.1%) on serotonin-selective reuptake inhibitor antidepressants (SSRIs), 10 (3%) on tricyclic antidepressants, 76 (22.6%) on ACE inhibitors, 66 (19.6%) on beta-blockers, 39 (11.6%) on diuretics and 29 (8.6%) on calcium channel blockers (Table 1). Motor UPDRS scores were obtained in 275 patients, 101 OFF (average 26.00 ± 13.34) and 174 ON (17.33 ± 10.74). A total NMS score was obtained in 224 subjects and was on average 7.85 ± 2.87. The mean autonomic NMS score (obtained in 249 subjects) was 2.94 ± 1.56.

3.2. Prevalence of constipation

Two hundred five patients (61%) reported constipation. Subjects with and without constipation were comparable for clinical and demographic characteristics and comorbidities (Table 1), except for age, PD duration and severity, as measured with motor UPDRS and NMS scores. Subjects reporting constipation were older (69.97 ± 9.85 vs. 66.09 ± 11.41, p value = 0.001) and had longer disease duration (8.28 ± 5.77 vs 6.17 ± 5.73, p value = 0.001). Average OFF and ON UPDRS III scores were significantly higher in patients with constipation (28.34 ± 14.99 and 19.47 ± 11.71, respectively) when compared to PD patients without constipation (22.84 ± 10.05, p value = 0.04 and 13.64 ± 7.59, p value <0.0001). Average total and autonomic NMS scores were significantly higher in patients with constipation (8.63 ± 2.92 and 3.30 ± 1.62, respectively) as compared to PD patients without constipation (6.68 ± 2.36, p value <0.0001 and 2.40 ± 1.29, p value <0.0001 respectively). LED was significantly higher in patients with constipation (701.94 ± 586.72) as compared to PD patients without constipation (422.55 ± 469.604, p value <0.0001).

Only pharmacological treatment with beta-blockers and dopaminergic agents showed significant differences between PD patients with and without constipation. In the group reporting constipation, 158 patients (77.1%) were treated with levodopa and 73 (35.6%) were treated with dopamine agonists with a higher prevalence than in non-constipated PD patients (55% and 22.9%, respectively, p values <0.0001). On the other hand, the percentage of patients treated with beta-blockers was significantly higher in the subgroup without constipation (29%) as compared to patients with constipation (13.7%, χ^2 test p value = 0.001) (Table 1). Among