Parkinsonism and Related Disorders 35 (2017) 48–54

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

The patient's perspective: The effect of levodopa on Parkinson symptoms

Heidemarie Zach [a, b, *], Michiel Dirkx [a], Jaco W. Pasman [a], Bastiaan R. Bloem [a], Rick C. Helmich [a]

[a] Radboud University Medical Centre, Donders Institute for Brain, Cognition and Behaviour, Department of Neurology, Nijmegen, The Netherlands
[b] Department of Neurology, Medical University of Vienna, Vienna, Austria

ARTICLE INFO

Article history:
Received 7 July 2016
Received in revised form
13 October 2016
Accepted 23 November 2016

Keywords:
Parkinson's disease
Visual analogue scale
Tremor
Levodopa-effect
Cognitive co-activation

ABSTRACT

Background: Dopaminergic medication adjustments in Parkinson's disease are often solely based on patient reports. However, it is unclear how well patient-based ratings of the levodopa response correlate with clinician-based ratings, and whether this correlation differs between motor symptoms. Here we compare patient-clinician agreement for the effect of levodopa on resting tremor and bradykinesia/rigidity. Furthermore, given patients' reports that tremor is most troublesome during stress, we test for differences in patient-clinician agreement between tremor at rest and stress-induced tremor.
Methods: We included 42 tremulous Parkinson patients, who were clinically rated (using the MDS-UPDRS) in a practically defined OFF-state and after levodopa-benserazide 200/50 mg. Using accelerometry, we quantified the effect of dopaminergic medication and behavioral context (rest vs. cognitive stress) on tremor intensity. Patients rated medication effects on tremor and bradykinesia/rigidity using visual analogue scales.
Results: There was only moderate patient-clinician agreement for the effect of levodopa on bradykinesia/rigidity ($R^2 = 0.18$; $p < 0.01$), and a tendency towards larger agreement for tremor ($R^2 = 0.44$; $p < 0.001$; difference between correlation coefficients: $z = 1.64$; $p = 0.051$). Patient ratings of tremor changes correlated significantly better with accelerometry for tremor during cognitive stress ($R^2 = 0.35$; $p < 0.001$) vs. tremor at rest ($R^2 = 0.12$; $p < 0.05$; difference: $z = -2.35$, $p < 0.01$).
Conclusion: The moderate correlations between patient ratings and clinical/accelerometry changes indicate the need for methods to better monitor symptom severity and impairments in daily life, for example wearable sensors. Our findings also suggest that context matters: Parkinson patients' subjective experience of levodopa effectiveness on tremor was largely based on the ability of levodopa to reduce tremor during cognitive stress.

1. Introduction

Parkinson's disease is a progressive neurological condition that requires constant medication adjustments. In busy clinics, where there is not always time to perform a careful neurological assessment, such medication adjustments are often mainly or even solely based on patient reports. This makes it crucial to conceive how well clinical and patient estimations correlate and which factors influence the patient's judgments about medication effectiveness. A better understanding of these factors may have impact on clinical practice (e.g. dosage adaptations), but also on the use of subjective assessment scales, like visual analogue scales (VAS), in scientific research [1].

Moving away from a strictly clinician-based decision model to a more holistic view (that also includes the patient's opinion), some studies have correlated these two perspectives [2]. Studies investigating dyskinesia and disability seem contradictory to some extent. Several studies found *under*estimation of symptoms or even *anosognosia* in PD patients, especially with regard to dyskinesia. This underestimation might be explained by subcortical impairment as well as dopaminergic overstimulation of mesocorticolimbic pathways in ON state [3–5]. Similarly, cognitively impaired patients in advanced stages of PD *under*estimate the

* Corresponding author. Medical University of Vienna, Dept. of Neurology, Waehringerstrasse 18-21, 1090 Vienna, Austria.
E-mail address: heidemarie.zach@meduniwien.ac.at (H. Zach).

http://dx.doi.org/10.1016/j.parkreldis.2016.11.015
1353-8020/

degree of impairment in activities in daily life [3,4,6]. However, not all evidence points in the same direction: it has also been reported that cognitively impaired patients in advanced stages tend to *over*estimate their disability in daily life [7].

While patients tend to underestimate many symptoms, the reverse is true for tremor. Parees and colleagues found *over*-estimation of tremor time and severity in psychogenic and organic tremor patients (including PD patients). While psychogenic tremor patients reported 65% more tremor than objectified by actigraphy, organic tremor patients reported tremor 'more accurately', but still overestimated severity and time by 28% [8]. Recently, Parveen and colleagues investigated agreement about six motor characteristics between patient and proxy ratings, which were completed by a caregiver and a clinical rater. They only found strong correlations between patients' estimations and clinical ratings (VAS vs. UPDRS) for 'externally observable' symptoms such as gait and rest tremor but not for bradykinesia and rigidity. Also here, patients generally perceived significantly more rest tremor than what was estimated by the clinical rater (patient's VAS vs. clinical rater's VAS) [9].

Only very few studies related patients' perceptions to objective measurements with respect to medication effects in the field of movement disorders. In a recent study in essential tremor (ET) patients, the authors correlated the clinician based results of the Fahn-Tolosa-Marin rating scale (TRS) [10] with VAS ratings OFF and ON medication and found only modest correlations [11]. There are no comparable studies for PD. Previous work in PD mainly focused on describing differences in the objective (clinician-rated) levodopa response of different PD symptoms. These studies report more variable and inconsistent response to levodopa in resting tremor (i.e. range between 0% and 80% tremor improvement) [12]. Compared to this, rigidity and bradykinesia show a more consistent response rate of 20%–70% [13–16]. However, it is unclear whether PD patients individually experience this distinction in the same way. Furthermore, it is unclear which factors influence patient-clinician agreement for levodopa effectiveness on tremor. Knowledge about these factors may help clinicians to adjust dopaminergic medication in such a way that patients perceive optimal benefit for their tremor. This is especially clinically relevant in early PD patients, as tremor is rated as their second most bothersome symptom [17].

Here we investigate the association between patient-ratings (VAS) and objective medical assessments (clinimetrics and accelerometry) of the levodopa effect on two Parkinson symptoms: resting tremor and bradykinesia/rigidity. First, we compared patient-clinician agreement for two different contexts: tremor at rest vs. tremor during cognitive stress. This was done because many patients report greater tremor under stressful circumstances [18]. Second, we compared patient-clinician agreement between tremor and bradykinesia/rigidity. This was done to test whether the relative underestimation of bradykinesia/rigidity vs. tremor by PD patients [9] also extends to the effect of dopamine on these two symptoms. We hypothesized that patient-clinician agreement is stronger for tremor under stress than for tremor at rest, and stronger for tremor than for bradykinesia/rigidity.

2. Methods

2.1. Study population

We enrolled 43 patients (27 men; mean age: 63 years; range: 38–81) with PD, diagnosed according to the UK Brain bank criteria [19], in an electrophysiological study at the Parkinson Center (ParC), Radboud University Medical Center, Nijmegen. All patients had a history of mild to severe resting tremor and were included after assessment by a movement disorders specialist. Only patients with a Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) resting tremor score (item 17) of $\geq$1 points in at least one arm were included. Exclusion criteria were: neurological co-morbidity, signs of psychogenic tremor (e.g. entrainment and distractibility), known allergy against levodopa-benserazide or domperidon, and significant cognitive impairment (Mini Mental State Examination (MMSE) score <24 or frontal assessment battery (FAB) < 12) [20,21]. Out of 43 patients, one patient was excluded because of signs of psychogenic tremor. All analyses were performed on the remaining 42 patients.

The study was approved by the local Ethics Committee and was performed according to the standards of the 1964 Declaration of Helsinki. All participants gave written informed consent prior to their inclusion. Patients were clinically assessed using the MDS-UPDRS-part III [22] and the Hoehn and Yahr Scale (H&Y) [23]. Three patients did not use Parkinson medication, the others used dopaminergic medication (levodopa and dopamine agonists; average daily levodopa equivalent: 489 mg; range: 0–1500 mg) and two patients were on anticholinergics. Five patients used beta-blockers for hypertension and/or tremor, however only one patient used a tremor-relevant dose (propranolol 80 mg twice daily). Patient characteristics are listed in Table 1.

2.2. Design

Patients were evaluated twice on one day, both before (OFF medication) and after a levodopa challenge (ON medication). Cognitive characteristics were measured once, using the MMSE and the FAB.

2.3. Levodopa-challenge

All patients were evaluated after overnight fasting and in a practically defined OFF-state, i.e. more than 12 h after intake of their last dose of dopaminergic medication and more than 24 h after anticholinergics or beta-blockers [24]. For the ON-state assessment, the patients first received 10 mg domperidon to reduce possible side effects and to improve gastro-intestinal absorption. This was followed by a standardized dose of 250 mg dispersible levodopa-benserazide 1 h later [24]. The first tremor assessment started on average 50 min (range: 42–59 min) after taking levodopa. Rigidity and bradykinesia were clinically assessed using the MDS-UPDRS (item 3–11 &14).

2.4. Medical assessments

2.4.1. Clinical assessment

Tremor was assessed clinically with items 15–18 of the MDS-

Table 1
Clinical characteristics.

Age (years)	63 (38–81)
Sex	15 F, 27 M
HY-stage (median)	2 (1.0–3.0)
Disease duration (years)	4.1 (0.5–10)
MMSE	29 (24–30)
FAB	17 (14–18)
TRS-C	5.8 (±0.8)
Levodopa equivalent at home (mg/d)	489 (0–1500)

If not indicated otherwise, data are mean (range) of 42 tremor-dominant Parkinson patients.
H&Y-stage: Hoehn and Yahr stage (score 0–5), MMSE: Mini Mental State examination (score 0–30), FAB: Frontal Assessment Battery (score 0–18). TRS-C: Tremor rating scale part C (score 0–32). For HY-stage and TRS-C, higher scores indicate worse functioning. For both FAB and MMSE, lower scores indicate worse functioning. The scores were evaluated OFF medication.