Parkinsonism and Related Disorders 19 (2013) 693–697

Contents lists available at SciVerse ScienceDirect

Parkinsonism and Related Disorders

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

Rest tremor suppression may separate essential from parkinsonian rest tremor

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ARTICLE INFO

Article history:
Received 23 November 2012
Received in revised form
11 February 2013
Accepted 18 March 2013

Keywords:
Parkinson rest tremor
Essential tremor
Blinded review

ABSTRACT

Rest tremor at 4–6 Hz is typical for classical rest tremor (PT) of Parkinson's disease (PD). But rest tremor also appears in other tremor syndromes and may therefore cause a misdiagnosis. In this study we evaluated if suppression of tremor during movement onset is a characteristic feature of Parkinsonian Tremor distinguishing PT from Essential tremor (ET) and if this sign can be reliably diagnosed.

Clinically diagnosed patients with PT ($n = 44$) and ET ($n = 22$) with rest tremor were included. Video sequences were recorded according to a standardized protocol focusing on the change of tremor amplitude during transition from rest to posture (test 1) or to a target-directed movement (test 2). These videos were assessed for rest tremor suppression by 4 reviewers (2 specialists and 2 residents) blinded to the clinical diagnosis and were compared to the personal assessment of an unblinded movement disorder specialist.

Rest tremor suppression was found in 39/44 PD patients and in 2/22 patients with ET during the personal assessment. Rest tremor suppression showed a high sensitivity (0.92–1.00) and an acceptable specificity (0.69–0.95) for PD tremor in both tests. The interrater-reliability of the video-sequences was good to very good (κ 0.73–0.91). Less than 3% of the video sequences were misclassified.

We conclude that the assessment of the suppression of rest tremor during movement initiation is a simple and reliable tool to separate PT from rest tremor in ET also suggesting that the mechanisms of rest tremor in these two diseases are different.

1. Introduction

Tremors are the most common movement disorders but their classification remains a challenge because most diagnostic entities rely on clinical criteria and only for few tremors objective, confirmative criteria are available. The Movement Disorder Society has introduced a classification of tremors simplifying the differential diagnosis of tremor [1] by taking into account the affected body parts, the main tremor frequency and the movement condition activating tremor but overlapping tremor frequencies and activation conditions prevent an unequivocal classification.

This applies in particular for tremor at rest which is considered typical for Parkinson's disease (PD). Rest tremor is found in up to 75% of PD patients at some time point in the course of their disease [2] but advanced essential tremor also may come with a low frequency resting tremor [3,4] which was to our knowledge explicitly described for the first time in 1987 [5,6]. Misdiagnosis is common in up to 20–30% of patients [7,8]. The accurate diagnosis is key for prognosis and treatment selection depends on the cause of tremor.

Clinical observations suggest that rest tremor in essential tremor and PT may be separated by grading tremor suppression during movement onset [1]. Rest tremor of PD was reduced in amplitude or showed complete cessation while this is not the case in essential rest tremor. It is the hypothesis of this paper that this suppression of rest tremor is separating rest tremor of PD from the rest tremor of ET. This study was designed to blindly assess this suppression in a group of patients with PT in comparison to ET patients with rest tremor.

2. Methods

2.1. Subjects

Consecutive patients with PD or ET were recruited and examined at the outpatient clinic of the Department of Neurology, Kiel University, (January 2006 to April 2007). All patients showed tremor at rest or/and during posture. The procedure was approved by the Local Ethical Committee (reference no. Az. A103/06), and all individuals gave written informed consent.

2.2. The clinical tremor diagnosis

The clinical diagnosis of each patient was based on all the available clinical knowledge. For the patients with PD the British Brain Bank Criteria [9] were used;

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http://dx.doi.org/10.1016/j.parkreldis.2013.03.013

as well as presence of tremor at rest, MRI/CCT brain scan for exclusion of symptomatic Parkinsonism and Datscan in questionable cases. ET was diagnosed according to the Consensus Statement of the Movement Disorder Society [1] and all patients fulfilled the Tremor Research Investigation Group criteria for definite essential tremor [10].

All patients were personally screened and examined by an experienced movement disorder expert (FP). Severity of tremor, especially focusing on rest tremor, was scored for all patients with the Fahn–Tolosa–Marin Tremor Rating Score (TRS) [11]. PD patients were rated with the UPDRS [12], and the clinical staging of Hoehn and Yahr [13]. All patients were asked to withdraw medication possibly influencing intensity of tremor 12 h prior to examination. Subsequently, a standardized tremor recording including accelerometry and surface EMG [14] was performed to document the occurrence of rest tremor. The clinical assessment of rest tremor served as "gold standard" for further evaluation. Patients who did not show rest tremors during clinical assessment were excluded from further evaluation (see Web-Attachment Fig. A).

2.3. Video recording and clinical assessment of rest tremor suppression

For video-taping the patients face and body were covered with a black drapery except for one arm. Videotapes of all patients were recorded with a video recorder showing two sequences:

Test 1: Patient sitting with the forearm resting on the armrest of the chair. The examiner did provoke a stable rest tremor by asking the patient to count backwards in steps of 7 from 100 [15]. Rest tremor intensity was scored by the rest tremor item of the TRS. Once the patient exhibited rest tremor he was asked to lift and stretch out his arms at the shoulder level (Fig. 1).

Test 2: Same starting point as test 1. Once a stable rest tremor was present patients were asked to touch a button with their index finger positioned in a comfortable position at shoulder level.

The unblinded investigator assessed the change of tremor amplitude compared to the resting position during movement onset with the naked eye from the camera location. Tremor amplitude changes (tremor rating scale change, TRS-change) were rated according to four possibilities: increase, decrease, complete suppression, or no change of tremor amplitude. The patients' arm with higher amplitude was recorded and rated.

2.4. Video rating

Short sequences (15 s) of videos were presented randomly and rated by two movement disorders experts and two neurological residents without special experience in movement disorders using the TRS at rest and evaluating the TRS-change. All raters were blinded to medical history or symptoms other than tremor of the study population. All ratings were performed independently. Blinded reviewers scored 5 training patients with feedback before the session.

2.5. Statistics

Data were analyzed by chi-square (χ^2) tests (categorical variables) and Student's t test (continuous variables). A Mann–Whitney U Test was used for not normally distributed data of two independent groups. p values <0.05 were considered significant. The diagnostic value of the clinical tests for PT (sensitivity, specificity, positive and negative predictive value) was calculated. Interobserver reliability between two raters was assessed with the Cohen's kappa coefficient (κ) for categorical variables. Because uniform rules are lacking how to interpret kappa values we used the criteria proposed by Landis et al. [16] classifying $\kappa < 0.2$ as poor, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as good, and 0.81–1.00 as very good agreement. All statistical procedures were performed with SPSS (Version 15.0).

3. Results

3.1. Clinical data

44 patients with PD (14 female, 30 male) and 31 patients with ET (9 female, 22 male) were screened for this study.

All PD patients had rest tremor and Parkinsonian features like bradykinesia, rigidity and continuous asymmetry of symptoms. MRI or CT brain imaging was available in all but 4 PD cases and did not reveal structural abnormalities. Pathological DAT-scans were available of 10 PD patients. All PD patients had a history of rest tremor but could not be provoked in one of the tests in 2 different cases.

All patients of the ET group had a longstanding nearly symmetrical bilateral action tremor lasting for at least 10 years in all but 2 cases. 9 ET-patients had no rest tremor in both tests during clinical examination and were excluded from further analysis. Finally rest tremor occurred in 22 ET cases in test 2 and in 20 cases in test 1. 14 patients with ET with rest tremor had a family history of ET. 13 patients reported that their tremor was reduced by drinking alcohol while 1 case had no response to alcohol and 8 cases did not know. MRI or CT scans of the brain were available in 17 ET patients without relevant structural lesions. Demographics, unblinded clinical and neurophysiological assessment of the patients with rest tremor are shown in Table 1. PD patients were significantly older at tremor onset. ET cases had significantly more relatives suffering from tremor within their families (Table 1). Clinical features of each PD and ET patient are described in the Web-Attachment (Table A–B).

3.2. Clinical and neurophysiological assessment

Rest tremor was present in all PD patients ($n = 44$) and ET-patients ($n = 22$) on clinical examination either in the 1st or in the 2nd test. Accelerometric and EMG tremor analysis confirmed rest tremors of PD patients and ET patients. We failed to provoke rest tremor in two different PD patients in one test each and in 2 ET patients in test 1. Hence, rest tremor was observed in 43 PD patients in both tests and in 20 respectively 22 ET patients in test 1 and test 2. As shown in Table 1 the rest tremor amplitude was significantly higher in the PD group in both tests, both on clinical assessment with the TRS and measured accelerometrically. Rest tremor frequency was also significantly different between the two groups with lower frequencies in the PD group.

During unblinded clinical assessment (gold standard) of the 1st test a reduction of rest tremor was observed in 39 (90.7%) of the PD patients with rest tremor; 24 (55.8%) of them had a complete suppression of rest tremor, 15 (34.9%) had a reduction of amplitude and 4 (9.3%) PD cases showed no change in tremor severity. Suppression of essential tremor amplitude was found in test 1 only in 2 (6.5%) of the 20 ET patients. 10 ET patients (50.0%) showed no

Fig. 1. An example of the course of action of the 1st test. The patient was sitting in a chair with forearms resting relaxed on the back of chair. A stable rest tremor was provoked. Rest tremor severity was scored. The patient was asked to lift subsequently his arm until he had reached shoulder level. At movement onset the change of rest tremor severity was scored. This sequence lasted approximately 15 s. 2nd test was similar but during the 2nd phase the patient had to perform a target-directed movement.