Parkinsonism and Related Disorders 30 (2016) 23–28

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

How typical are 'typical' tremor characteristics? Sensitivity and specificity of five tremor phenomena

A.M.M. van der Stouwe [a, b, *], J.W. Elting [a, c], J.H. van der Hoeven [a, c], T. van Laar [a], K.L. Leenders [a], N.M. Maurits [c], M.A.J. Tijssen [a]

[a] Department of Neurology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[b] Department of Neurology, Isala Clinics, Zwolle, The Netherlands
[c] Department of Clinical Neurophysiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

ARTICLE INFO

Article history:
Received 31 May 2015
Received in revised form
25 May 2016
Accepted 14 June 2016

Keywords:
Essential tremor
Enhanced physiological tremor
Functional tremor
Entrainment
Tremor phenomenology

ABSTRACT

Introduction: Distinguishing between different tremor disorders can be challenging. Some tremor disorders are thought to have typical tremor characteristics: the current study aims to provide sensitivity and specificity for five 'typical' tremor phenomena.

Methods: Retrospectively, we examined 210 tremor patients referred for electrophysiological recordings between January 2008 and January 2014. The final clinical diagnosis was used as the gold standard. The first step was to determine whether patients met neurophysiological criteria for their type of tremor. Once established, we focused on 'typical' characteristics: tremor frequency decrease upon loading (enhanced physiological tremor (EPT)), amplitude increase upon loading, distractibility and entrainment (functional tremor (FT)), and intention tremor (essential tremor (ET)). The prevalence of these phenomena in the 'typical' group was compared to the whole group.

Results: Most patients (87%) concurred with all core clinical neurophysiological criteria for their tremor type. We found a frequency decrease upon loading to be a specific (95%), but not a sensitive (42%) test for EPT. Distractibility and entrainment both scored high on sensitivity (92%, 91%) and specificity (94%, 91%) in FT, whereas a tremor amplitude increase was specific (92%), but not sensitive (22%). Intention tremor was a specific finding in ET (85%), but not a sensitive test (45%). Combination of characteristics improved sensitivity.

Conclusion: In this study, we retrospectively determined sensitivity and specificity for five 'typical' tremor characteristics. Characteristics proved specific, but few were sensitive. These data on tremor phenomenology will help practicing neurologists to improve distinction between different tremor disorders.

1. Introduction

Although tremor is the most common movement disorder, distinguishing between different tremor disorders can be challenging [1,2]. The phenomenology of tremor is complex, involving a broad range of signs and symptoms. Some tremor disorders seem to have a typical tremor characteristic that points to the diagnosis, but if sensitivity and specificity of these presumed hallmarks are unknown, their significance remains uncertain. In the present study we aimed to provide sensitivity and specificity numbers for five 'typical' tremor characteristics.

Firstly, a frequency decrease after loading or weighing of the tremulous hand can be found in enhanced physiological tremor (EPT). This phenomenon has been long known [3] and is also reported in normal subjects [4]. The frequency shift is thought to appear because EPT is caused partly by mechanical reflex oscillation, which is dependent of the hand's resonant frequency and therefore changes with increased inertial loading [5]. The frequencies of tremor disorders that are considered to be generated by a central oscillator are supposed to be invariable upon loading [6]. However, no studies on the sensitivity and specificity of this phenomenon exist.

Secondly, we aimed to investigate three phenomena that appear

* Corresponding author. Department of Neurology, University Medical Center Groningen, Hanzeplein 1, 9700 RB, Groningen, The Netherlands.
E-mail address: a.m.m.van.der.stouwe@umcg.nl.nl (A.M.M. van der Stouwe).

http://dx.doi.org/10.1016/j.parkreldis.2016.06.008
1353-8020/© 2016 Elsevier Ltd. All rights reserved.

to be typical of functional tremor (FT): an amplitude increase after loading of the tremulous hand [7], entrainment [[7–9] and distractibility [10,11]. These characteristics have been described in previous small studies, and are considered positive symptoms for the diagnosis of FT. On the other hand, it is known from clinical experience that these features occasionally occur in 'organic' tremor patients, which raises the question how specific these characteristics really are [12].

Lastly, intention tremor, which is tremor increasing during goal-directed movement, is known to occur in some essential tremor (ET) patients [13], but is atypical in most other tremors. A recent study reported intention tremor in 28% of ET patients versus only 4% of Parkinson's disease patients [14]. We set out to extend these numbers to the general tremor population.

In this study, we retrospectively determined sensitivity and specificity for typical tremor phenomena, to extend the available data on clinical tremor phenomenology and assist clinicians in their neurological examinations and diagnosis.

2. Methods

2.1. Subjects

We searched the database of the department of Clinical Neurophysiology of the University Medical Center Groningen, a tertiary referral center, for patients who had undergone polymyography as part of the diagnostic work-up for upper limb tremor. All subjects had to be > 18 years old. The starting point was January 1st, 2014, and we continued the search until 2008, when we had identified 50 subjects in each of the three groups with whom we planned to test specific tremor characteristics (EPT/ET/FT). We also included all patients with other tremor diagnoses in order to achieve a diverse general tremor population as a control group.

2.2. Clinical diagnosis

We used the attending neurologist's most recent clinical diagnosis as the gold standard: the final diagnosis after polymyography and in some cases, imaging or laboratory testing. Patients were not included if the neurologist had to date been unable to differentiate between two disorders ($n = 10$). Another exclusion criterion was lack of a final clinical diagnosis, if correspondence was unavailable. From the clinical records, we recorded: age, sex, primary diagnosis pre-polymyography, and the final clinical diagnosis.

2.3. Clinical neurophysiology testing

In our center's tremor-specific polymyography assessment, tremor is evaluated at rest, during different postural positions, and while performing specific tasks (described below). All our data are derived from reports of these standardized electrophysiological recordings, written by two experienced clinical neurophysiologists (JWE, JvdH). They based their reports on continuous recordings of accelerometry, EMG, and video. EMG was recorded with Ag/AgCl surface electrodes placed over four muscle groups of each arm: the wrist and elbow flexors and extensors. Accelerometers were placed on the dorsal side of both hands. All frequency analyses were based on accelerometry, using fast Fourier transformation. Data were recorded using Brain RT software (OSG BVBA, Rumst, Belgium).

Table 1 summarizes the criteria used in our clinic for the clinical neurophysiological diagnosis [15–17]. For each group, we calculated the percentage of patients who met each criterion.

To assess the influence of polymyography on diagnosis, we compared the clinical pre-polymyography diagnosis, the neurophysiological diagnosis derived from polymyography, and the final clinical post-polymyography diagnosis to determine how the outcome of the neurophysiological testing affected the diagnosis.

2.4. 'Typical' tremor phenomena

The five specific tremor characteristics which we aimed to test for sensitivity and specificity are described below. These tremor characteristics are routinely assessed: results could be derived from the clinical neurophysiology reports.

Arm Loading was achieved by wrapping two or (in frail or elderly patients) one 500 g weight, depending on the patient's frailty strength, around the patient's wrist using flexible weights equipped with velcro. We recorded whether there was a *decrease in tremor frequency* (>1 Hz) upon loading, and/or an *increase of tremor amplitude* compared to the unloaded state, as reported by the neurophysiologist.

Entrainment was investigated while the most-affected hand was held in the position that evoked maximal tremor. Patients were instructed to imitate tapping motions with their least-affected hand at the same speed as the laboratory technician, who would vary the frequency between ±1–4 Hz. A positive entrainment test result was recorded in the case of a notable tremor frequency shift (decrease>1 Hz) of the contralateral hand, or temporary tremor suppression (assessed with accelerometry/EMG/video).

Distractibility was assessed formally with hands held in the position that evoked maximal tremor. Patients were instructed to serially subtract seven from a hundred out loud (100, 93, 86, etc.). In addition, distractibility was investigated informally during conversation and task instruction. We chose to combine these assessments because it is our impression that not all patients are sufficiently distracted by formal yet simple tasks: assessment during the rest of the consultation is of equal importance. Distractibility was defined as a notable frequency shift (decrease>1 Hz) or temporary tremor suppression during formal or informal mental distraction.

Intention tremor was assessed with finger-to-nose maneuvers, where patients were instructed to move the index finger of their outstretched arm to the tip of their nose. If tremor amplitude increased as the patient's finger approached the nose this was scored as a positive test result.

In principle, all tests were performed on all patients (missing data <10 per characteristic), with the exception of loading, which was not performed in 7 PD patients with pure resting tremor, as the weight does not affect an arm that is fully supported against gravity.

2.5. Statistical analysis

Patient and tremor characteristics were compared between groups using Chi-square tests for gender and Kruskal-Wallis tests for all continuous, not-normally distributed data in SPSS 20 (SPSS, Chicago, IL). In case of differences between groups, post-hoc testing was performed using Mann-Whitney tests. We compared the frequency of positive test results for each tremor characteristic with Fisher's exact tests, and considered results significant if $p < 0.05$. Next, we calculated sensitivity (#true positives/#patients in the 'typical' tremor group) and specificity (#true negatives/#patients *outside* the 'typical' tremor group) for each test, along with positive likelihood ratios (LR+) and negative likelihood ratios (LR-). LR+ (sensitivity/(1-specificity)) can range from 1 to infinity and concerns positive test results: the higher LR+, the stronger a positive test result indicates acceptation of the diagnosis. LR- ((1-sensitivity)/specificity) can range from 0 to 1, and concerns negative test results: the lower LR-, the stronger a negative test result indicates rejection of the diagnosis.

To place the phenomena in a broader perspective and improve