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CHAPTER 2

HOW TYPICAL ARE 'TYPICAL' TREMOR CHARACTERISTICS?

SENSITIVITY AND SPECIFICITY OF FIVE TREMOR PHENOMENA

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ABSTRACT

BACKGROUND: 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 in the period January 2008-January 2014. The final clinical diagnosis was used as gold standard. The first step was to determine whether patients met the 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 with 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 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.

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

INTRODUCTION

Although tremors are the most common movement disorders, distinguishing between different tremor disorders can be challenging (1, 2). The phenomenology of tremor is complex, involving a broad variety 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 establish how well the clinical tremor diagnosis met the clinical neurophysiological criteria. Furthermore, we aim to provide sensitivity and specificity numbers for five 'typical' tremor characteristics.

Firstly, a frequency decrease after loading or weighing of the tremulous hand is 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 considered to be caused partly by mechanical reflex oscillation. This oscillation 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 aim to investigate three phenomena that seem 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 to be positive symptoms for the diagnosis of FT. On the other hand, it is known from clinical experience that these features occasion-ally 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 essential tremor (ET) (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 would like to extend these numbers to the general tremor population.

In this study, we retrospectively determine sensitivity and specificity for typical tremor phenomena, to extend the available data on clinical tremor phenomenology and aid clinicians in their neurological examinations and diagnostic process.

METHODS

SUBJECTS

We searched the database of the department of Clinical Neurophysiology of the University Medical Center Groningen, a tertiary referral centre, for patients who had undergone a polymyography as part of the diagnostic work-up for upper limb tremor. All subjects had to be >18 years old. The search started at January 1st, 2014, and continued until the three groups of which we intended to test specific tremor characteristics (EPT/ET/FT) each contained 50 subjects (January, 2008). Patients with other tremor diagnoses were also included to attain a diverse general tremor population as a control group.

CLINICAL DIAGNOSIS

As a starting point, we took the most recent clinical diagnosis by the attending neurologist as the gold standard: the final diagnosis after polymyography and possibly imaging or laboratory testing. Patients were not in-

cluded if the neurologist had considerable doubt about the diagnosis: in case of a current impossibility to differentiate between two disorders. Another exclusion criterion was lack of a final clinical diagnosis, if correspondence was unavailable. For each subject, we recorded from their clinical records: age, sex, primary diagnosis pre-polymyography, and the final clinical diagnosis.

CLINICAL NEUROPHYSIOLOGY TESTING

In our centre's tremor-specific polymyography recording, tremor is assessed during rest, posture and specific tasks. All our data

TABLE 2.1. CLINICAL NEUROPHYSIOLOGICAL GUIDELINE.

	Criteria for electrophysiological diagnosis at our hospital	Prevalence*
EPT	Core criteria: • Unstable tremor frequency: change >1 Hz upon change of posture or loading • Predominantly distal tremor Supportive criterion: • High frequency (>7 Hz)	90% 78% 78%
ET	Core criteria: • Bilateral tremor during posture/action • Stable tremor frequency: <2 Hz variation throughout registration Supportive criterion: • Intention tremor	96% 94% 42%
FT	Core criterion: • Unstable tremor frequency: >1 Hz variation or temporal tremor suppression upon change of posture, mental distraction or entrainment Supportive criteria: • Increase in tremor amplitude upon loading	 94% 22%
PT	Core criteria: • Tremor at rest • Stable tremor frequency: <2 Hz variation throughout registration Supportive criteria: • Increase in tremor amplitude during mental tasks • Frequency between 4 and 7 Hz	95% 100% 39% 95%
DT	Core criteria: • Signs of dystonia, co-contraction between agonists and antagonists, overflow Supportive criteria: • Irregular tremor • Proximal tremor • Influence of sensory stimuli	33% 50% n.a. n.a.
CT	Core criteria: • Tremor predominantly during action • Intention tremor	100% 100%
HT	Core criteria: • Tremor present at rest, posture and action • Low frequency (<4Hz) Supportive criterion: • Intention tremor	100% 100% 100%

EPT: enhanced physiological tremor, ET: essential tremor, FT: functional tremor, PT: Parkinsonian tremor, DT: dystonic tremor, CT: cerebellar tremor, HT: Holmes tremor. *: prevalence in the study group with a corresponding final clinical diagnosis; for group information see Results section and Table 2, n.a.: not available, these criteria were not consistently reported.

is 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 wrist and elbow flexors and extensors. Accelerometers were placed on the dorsal side of both hands. All frequency analyses were based on accelerometry. Data was recorded using BrainRT software (OSG BVBA, Rumst, Belgium).

In Table 2.1 we have summarized the criteria used in our clinic for the clinical neurophysiological diagnosis (15-17). For each group, we calculated how many patients met these criteria.

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. In case of a change in diagnosis, we noted the nature of the conversion.

'TYPICAL' TREMOR PHENOMENA

We will describe the five specific tremor characteristics of which we aimed to test sensitivity and specificity in more detail. These are routinely assessed: results could be derived from the clinical neurophysiology reports.

Loading of the arm was realized by attaching one or two 500 g weights, depending on the patient's strength, to the patient's wrist. We recorded whether there was a decrease of tremor frequency (>1Hz) upon loading, and/or an increase of tremor amplitude compared to the unloaded condition, 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 scored in case of a notable tremor frequency shift (decrease>1Hz) of the contralateral hand, or temporary tremor suppression.

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.). Moreover, distractibility was investigated informally during conversation and instruction of tasks. 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 notable frequency shift (decrease>1Hz) or temporary tremor suppression during formal or informal mental distraction.

Intention tremor was assessed with finger-to-nose manoeuvres, 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.

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 calculated sensitivity and specificity for each test. We considered results significant if p<0.05.

To place the phenomena in a broader per-

spective and improve discriminative value, we combined tests (presence of tremor phenomena) with tremor frequency and frequency variability. In case of multiple significantly different tests for one diagnosis versus all others we investigated combinations. Cut-off values for tremor frequency and variability were first estimated based on visual inspection, and we calculated ROC-curves for frequencies between 6.0-7.0 Hz and frequency variability between 1.25-2.0 Hz at 0.25 Hz intervals: the combinations with the largest area under the ROC-curve (AUC), reflecting the highest discriminative value, are reported.

RESULTS

PATIENT CHARACTERISTICS

Two hundred-ten patients were included in this study (Table 2.2). Patients had a diagnosis of EPT (n=50), ET (n=50), FT (n=50), Parkinsonian tremor (PT, n=41), dystonic tremor (n=7), cerebellar tremor (CT, mostly MS-related, n=8) or Holmes or rubral tremor (HT, n=4). Gender distribution did not dif-

fer between groups. There was an age difference (p<0.001): EPT patients were younger than ET, FT and PT patients (all: p<0.001). Moreover, ET patients were older than FT (p<0.001) and PT patients (p=0.006).

CLINICAL NEUROPHYSIOLOGY

The final clinical diagnosis met with all (87%) or at least one (92%) of our core neurophysiological criteria in most cases. The supportive criteria were met less frequently (see Table 2.1). Median tremor frequency was 8.2 Hz in EPT patients, 5.8 Hz in ET patients, 5.3 Hz in FT patients and 5.4 Hz in PT patients (Table 2.2, Figure 2.1). There was a difference between patient groups (p<0.001): tremor frequency was higher in EPT compared to ET, FT and PT (all: p<0.001). Frequency variability was different between groups (p<0.001): frequency variability was higher in EPT (2.5 Hz) and FT (2.3) compared to ET (1.0) and PT patients (0.9) patients (all: p<0.001).

TABLE 2.2. PATIENT CHARACTERISTICS

	N	M/F	Age	Mean frequency	Frequency variability
EPT	50	30/20	44 (38)*	8.2 (2.0)*	2.5 (1.4)*
ET	50	29/21	71 (11)*	5.8 (0.8)	1.0 (0.4)
FT	50	27/23	60 (16)	5.3 (1.4)	2.3 (1.4)*
PT	41	24/17	59 (18)	5.4 (1.3)	0.9 (0.3)
DT	7	3/3	51 (37)	5.7 (4.4)	2.0 (1.3)
CT	8	4/4	43 (13)	5.0 (1.9)	1.0 (0.8)
HT	4	1/3	66 (42)	3.3 (0.6)	0.8 (1.0)

All values except gender are displayed as median (interquartile range). EPT: enhanced physiological tremor, ET: essential tremor, FT: functional tremor, PT: parkinsonian tremor, DT: dystonic tremor, CT: cerebellar tremor, HT: Holmes tremor. M/F: Male/Female. *Significant difference, direct post-hoc comparison between EPT, ET, FT and/ or PT (see text).
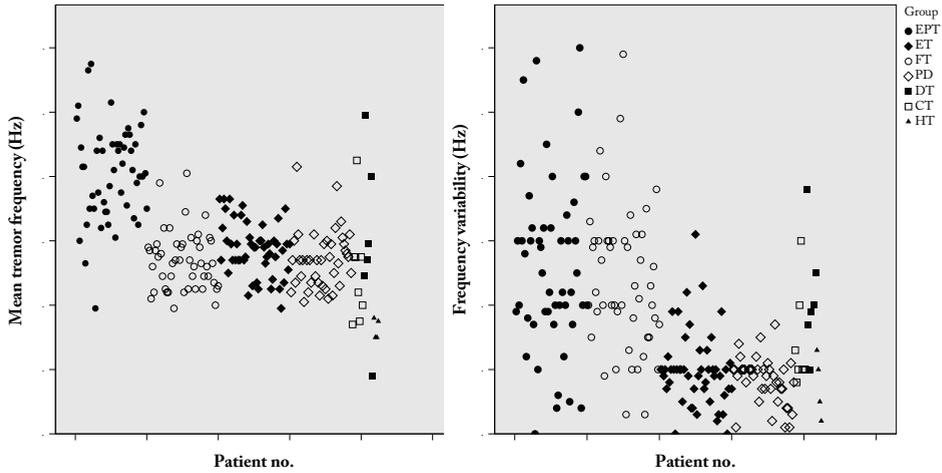
Figure 2.1. Mean tremor frequency (left) and tremor frequency variability (right) in Hz. ET: essential tremor, FT: functional tremor, PT: parkinsonian tremor, DT: dystonic tremor, CT: cerebellar tremor, HT: Holmes tremor.

INFLUENCE OF POLYMYOGRAPHY ON CLINICAL DIAGNOSIS

The diagnosis that topped the differential diagnosis pre-polymyography was confirmed by the polymyography in 70% of all cases. Contrarily, in 22%, the initial diagnosis changed. In those 45 cases, the incorrect pre-polymyography diagnosis was ET (n=21), EPT (n=10), PT (n=8), DT (n=2), tremor due to a structural lesion (n=2), neuropathic tremor (n=1), or myoclonus (n=1). These 45 incorrect diagnoses turned into a final clinical diagnosis, after polymyography and occasionally other testing, of FT (n=18), EPT (n=13), ET (n=8), PT (n=5), and HT (n=1) (Table 2.3). In a small number of patients (5%), the initial pre-polymyography diagnosis did not change, although the conclusion of the polymyography report suggested

TABLE 2.3. CHANGES IN DIAGNOSIS (N=45)

Pre \ Final	EPT	ET	PT	FT	HT	*Total*
EPT	-	6	0	4	0	*10*
ET	11	-	3	6	1	*21*
PT	2	2	-	4	0	*8*
DT	0	0	1	1	0	*2*
Structural lesion	0	0	0	2	0	*2*
Neuropathic	0	0	1	0	0	*1*
Myoclonus	0	0	0	1	0	*1*
Total	*13*	*8*	*5*	*18*	*1*	

Cases in which there was a difference between pre-polymyography diagnosis ('Pre': rows) and final diagnosis ('Final': columns).

TABLE 2.4. SENSITIVITY AND SPECIFICITY OF FIVE TYPICAL TREMOR CHARACTERISTICS.

	Sensitivity	Specificity
Frequency decrease upon loading in EPT	42%	95%
≥2 positive for EPT: • Frequency decrease upon loading • Frequency > 6 Hz • Frequency variability > 1.75 Hz	84%	94%
Amplitude increase upon loading in FT	22%	92%
Entrainment in FT	91%	91%
Distractibility in FT	94%	92%
≥2 positive for FT: • Entrainment • Distractibility • Frequency variability > 1.75 Hz	100%	93%
Intention tremor in ET	42%	85%

a different diagnosis (in 3/8 cases the final diagnosis was DT, in 2 cases ET, 1 case FT, 1 case EPT, 1 case PD). In 3% of the cases, the clinician added a so-called 'functional component' to the final diagnosis because of 'functional features' in an otherwise organic-considered tremor, for example 'PT with functional component'.

'TYPICAL' TREMOR CHARACTERISTICS

Enhanced physiological tremor

A decrease of tremor frequency upon loading was found in 42% of EPT patients, versus 5% of non-EPT patients (p<0.001). Test sensitivity for EPT was 42%, specificity 95% (Table 2.3). A score of at least 2 out of 3 positive tests from 1) frequency decrease upon loading, 2) tremor frequency >6 Hz, and 3) tremor frequency variability >1.75 Hz, resulted in increased test sensitivity for EPT of 84%, and specificity of 94% (AUC=0.946, p<0.001).

Functional tremor

An increase of tremor amplitude upon loading was seen in 22% of FT patients, versus 8% of non-FT patients (p=0.331).

Test sensitivity for FT was 22%, specificity was 92%. Entrainment occurred in 91% of FT patients, versus 9% of all other patients (p<0.001): test sensitivity for FT was 91%, specificity 91%. A decrease of tremor frequency or amplitude upon distraction was seen in 94% of FT patients, versus 8% of all other patients (p<0.001). Test sensitivity for FT was 94%, specificity 92%. A score of ≥2 out of 3 positive tests from 1) entrainment, 2) distractibility, and 3) tremor frequency variability >1.75 Hz, resulted in test sensitivity for FT of 100%, and specificity of 93% (AUC=0.985, p<0.001).

Essential tremor

We found intention tremor in 42% of ET patients, versus 15% of non-ET patients (p=0.000). Test sensitivity for ET was 42%, test specificity 85%. Test specificity was decreased by the occurrence of intention tremor in CT and HT patients: specificity increased to 92% after omission of CT and HT patients.

DISCUSSION

We retrospectively determined sensitivity and specificity for five presumed typical

tremor characteristics, by comparing prevalence of each phenomenon in 50 patients from the relevant tremor disorders versus patients from a diverse, general tremor population.

First, we detected that in 87% of our patients the final clinical diagnosis concurred with all our core clinical neurophysiological criteria. Supportive criteria for different tremor types were met less frequently, underpinning their role as secondary criteria. As some of the used clinical neurophysiological criteria are consensus-based (15), we are pleased to reinforce these parameters here.

The polymyography diagnosis supported the pre-registration clinical tremor diagnosis in the majority of cases, whereas the diagnosis changed in 22%. It is noteworthy to see what changes in diagnosis were made under the influence of the tremor-specific polymyograpy. In nearly half the cases where the diagnosis changed the initial diagnosis was ET. Apparently, we are quick to think of ET, which is fitting with ET's image as an over-diagnosed disorder (1, 2). Another point of interest is that FT was never an incorrect top differential, whereas of the incorrect diagnoses, 18 out of 45 changed into FT. We conclude that in our tertiary referral centre neurologists are conservative in diagnosing tremor as functional. This is understandable, but also dangerous, as a positive, unambiguous diagnosis is key in the treatment of functional disorders (21).

Regarding the 'typical' tremor phenomena, our findings reveal that a frequency decrease upon loading of the tremulous arm is specific for EPT (95%). However, it is not a sensitive test (42%): lack of a change in frequency is therefore not informative, but if the tremor frequency decreases this points to EPT. To our knowledge, this is the first study to report sensitivity and specificity numbers for this test. Sensitivity increases to 84% when

the effect of loading is combined with tremor frequency (>6 Hz) and frequency variability (>1.75 Hz). These results suggest that a scoring system of at least 2 positive tests out of 3 for EPT may be diagnostically useful.

Of the phenomena we investigated that are believed to be typical for FT, testing for distractibility was most useful. A noticeable frequency decrease or temporary tremor suppression upon distraction occurred in almost all FT patients, making this a very sensitive feature (94%), while at the same time the phenomenon was specific for FT (92%). Tremor distractibility has been described before in FT (10) and one study reported a sensitivity for mental distraction by means of a simple calculation task ("serial subtractions of 7") of 58.3% (11). We report a much higher sensitivity in the current study, probably because we assessed distractibility both formally with the same calculation task and informally throughout the registration.

The test for entrainment resulted in similar high sensitivity (91%) and specificity (91%), and is therefore also informative. Again, we report higher numbers than previous studies (7, 8) probably because we applied less formal testing: either true entrainment, a noticeable frequency shift, or temporary tremor suppression scored as entrainment. We consider these extended definitions of distractibility and entrainment appropriate because they represent what neurologists want to assess clinically: the influence of mental or motor tasks on the tremor.

Finally, testing for tremor amplitude increase upon loading was the least useful test for FT. Overall, the phenomenon was uncommon, and statistically, it did not occur significantly more often in FT than in other tremor disorders. Test sensitivity was very low (22%), although specificity was high (92%). Although a previous study (7) used a quantified accelerometry measure instead of our visual assessment of video/EMG/accelerometry

recordings, their results for sensitivity and specificity were highly similar: 33% and 92%. In general, we would like to point out that although all FT-tests have a high specificity, none reached 100%. As is known from previous work (7-9,11), 'functional' characteristics can occur in otherwise 'organic' tremor. In this study, we confirm that distractibility, entrainment and an increase of tremor amplitude after loading can all be seen in organic tremor. It is of course possible that an existing organic tremor is worsened by functional tremor. This was sometimes acknowledged by the neurologist, by adding 'plus a functional component' to their final diagnosis.

Overall, a combination of entrainment, distractibility and tremor frequency variability (>1.75 Hz) was most suited to classify FT patients. Scoring ≥2 positive test results out of 3 resulted in a test sensitivity of 100% and specificity of 93%, increasing the feasibility of diagnosing FT on positive findings instead of per exclusionem. This fits well with the current clinical approach of counting the positive rather than the negative symptoms in functional movement disorders (12).

Our data further reveal that intention tremor occurs in two out of five ET patients, which is in accordance with previous studies (13,18). We extended previous work on prevalence of intention tremor in ET versus PT patients (14) to the general tremor population, and found that intention tremor occurs in 15% of non-ET tremor patients. The feature was most common in CT and HT patients, which is to be expected as intention tremor is a sign of cerebellar disease, and in these disorders the cerebellum or cerebellar outflow-tract is affected (19,20). Omission of CT and HT patients increased test specificity to 92%. Therefore, a positive finger-to-nose test is informative in distinguishing ET from EPT, PT, DT, and FT, but not CT and HT.

There are two potential weaknesses that relate to our 'gold standard': the most recent clinical diagnosis. As the clinical diagnosis is partly based on features of which we set out to test sensitivity and specificity, there is a risk of a circular argument: patients are included in the EPT group because their tremor frequency decreases upon loading, and then we investigate loading as a diagnostic test for EPT. To test the extent of this potential problem, we performed a sub-analysis on the 70% of patients in whom the primary differential diagnosis was confirmed by the polymyography report, thus excluding changes in diagnosis due to the polymyography-findings. As sensitivity and specificity of the five characteristics hardly changed in this subgroup, we concluded that the diagnosis circular argument does not play a major role in our findings. Note that the final diagnosis did not rely solely on the characteristics we investigated, but also takes into account history taking, examination and imaging. Another weakness is that the clinical diagnosis may not have been correct in all cases. However, as most patients were seen by experienced movement disorders specialists, all underwent a tremor-specific polymyography, and MR- and PET-imaging were performed when indicated, we are confident that the vast majority of cases was assigned to the appropriate group.

Two final limitations that need to be noted are that patients with an inconclusive diagnosis were excluded. Finally, distractibility was investigated both informally and formally. This increases the sensitivity but may also increase bias.

A strength of this study is that characteristics were tested in a general tremor population, and not only in isolated groups such as ET vs PD. This makes it possible to relate the results to the actual clinical setting of a patient presenting with tremor. These data on tremor phenomenology will help practicing

neurologists to better distinguish between different tremor disorders.

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