

Clinical Review

My hands shake: Revisiting the assessment of tremor

Introduction

Tremor, an involuntary, rhythmic and oscillatory movement of a body part, is a frequent presenting symptom to general practice and by far the most common movement disorder presentation impacting up to 15% of such cases (1). A common initial pattern is symmetric upper limb involvement during posture and action. Although patients are often worried about Parkinson's disease (PD), PD tremor usually has easily recognisable features (2). This concern tends to lead to frequent referrals for specialist input despite an alternative diagnosis being more likely in a majority of cases. Essential tremor (ET), is the most common diagnosis given to patients with this presentation which is estimated to affect 0.4 to 6 percent of the general population (3). This may be an overestimate as the rubric of ET and the relationship between clinical features and underlying pathophysiology is uncertain. These aspects also potentially contribute to variable diagnostic and treatment outcomes (4). A recent Movement Disorders Society consensus on phenotyping charts a course towards more precise classification (5). This will be useful for research but also helps in clarifying common clinical syndromes seen in everyday practice. Here, we outline an approach to upper limb tremor presentations in adult patients developing on a previously proposed 3 cardinal question method for neck pain (6) while highlighting salient aspects of the consensus statement that could potentially aid in clinical stratification of cases.

Clinical assessment

History

Characterising the onset age, anatomical distribution (head, voice, hands, and symmetry) and temporal evolution of the tremor is important, forms the first step of the assessment and aids in determining the underlying syndrome (outlined in subsequent sections). A key aspect to establish early is if the tremor results in functional impairment as this will determine if treatment is warranted

(all current treatment options are symptomatic i.e. non disease modifying) (7)(8). Useful questions to establish this include when the tremor is worst (writing, using a cup, relaxing) and whether assistance is needed e.g. with preparing food. Then, relevant family and past histories (medication exposure, alcohol and drug sensitivity) as well as the presence of other neurological symptoms (e.g. slowing up, gait disturbance, muscle stiffness and aches) should be explored. The latter aspects are more typical of PD than ET and can provide early diagnostic clues in differentiating these 2 conditions. Some tremorgenic medications to consider include salbutamol, ciclosporine, haloperidol, lithium, and valproic acid. Caffeine intake, anxiety and alcohol use can result in or exacerbate pre-existing tremor and these aspects should be clarified on history taking. However, some forms of tremor are alcohol responsive so alcohol misuse may be secondary to an underlying neurological condition.

Examination

Observation is key and should continue throughout the consultation. This includes the patient's gait and movements when walking into the room particularly noting how easily they stand up (difficulty in parkinsonian syndromes), how far apart their feet are (broad stance implicates potential proprioceptive or cerebellar impairment), and if they take appropriately spaced strides (short strides in parkinsonian syndromes). Other parkinsonian features (reduced blinking, decreased facial expression, stooped posture), the location of the tremor and the presence of systemic signs (exophthalmos, goitre) may also be evident before the formal examination.

Defining tremor characteristics (frequency, amplitude and nature) are of little value though establishing changes in activation conditions is useful. This includes assessments at rest - limbs supported on the patient's lap (Figure 1A) and observing for tremor with distraction (counting backwards or complex subtractions), which is typical of PD tremor. Postural tremor is then assessed with both upper limbs outstretched (Figure 1B) and followed by the finger nose task (Figure 1E) looking for a kinetic or intention tremor. During the transition from rest to posture, reemergent

tremor (i.e. the tremor disappears and then re-appears) should be established (strongly suggestive of PD). Additional movements (dystonia or myoclonus) should also be noted. Definitions are outlined in table 1.

Co-existent limb Parkinsonism can be detected with finger taps (Figure 1C, D). Patients tap their thumb and index finger approximately 10 times. Small and slow movements suggest bradykinesia while taps progressively becoming smaller (decrement) or stopping imply PD. Rotation of the hand at the wrist to note for resistance (extrapyramidal tone) follows. Handwriting to assess for micrographia (small handwriting, progressively gets smaller) or writing tremor and functional impairment (e.g. pouring water from cup to cup) completes the examination. Exacerbation (or provocation) of tremor when pouring water from cup to cup is typical of essential and dystonic tremor.

Investigations

Tests to exclude symptomatic causes (thyroid, renal and liver function) should be performed in primary care. Additional tests may be pertinent but should be considered by specialists.

Syndromes, aetiologies and 'red flags'

A recent expert consensus proposal suggests an axes approach to organising clinical findings (5). This could potentially aid in conceptualising cases in practice rather than focusing purely on a diagnostic label though detailed utility of this approach would more likely be relevant in neurological practice. Axis 1 comprises efforts to define clinical features (i.e. a syndrome observed based on the history and examination) and axis 2 encompasses testing to determine the underlying aetiology. Axis 1 findings can reflect characteristic syndromes- *isolated tremor syndrome* (when mono-symptomatic) or *combined tremor syndrome* (when the tremor is associated with other clinical signs). The axis 2 cause identified is the underlying diagnosis rather than the syndrome defined. Both axes features should be regularly re-evaluated if initially not characteristic of an established diagnostic entity.

Different axis 2 aetiologies resulting in one or a variety of axis 1 syndromes is possible, and the converse holds true. We now consider upper limb syndromes, highlighting recent definition changes and features for referral (Table 2).

Essential tremor

Essential tremor is an isolated bilateral upper limb action tremor syndrome. Although co-existent tremor (head, voice, lower limbs) can occur, isolated tremor in these regions should not be regarded ET (5). Useful diagnostic features include tremor during action, including writing, holding a cup and saucer and pouring together with the absence of bradykinesia. A 3-year observation period during which the tremor is considered indeterminate has been proposed. This is to safeguard against the development of additional features and therefore alternate syndromes. If the onset is sudden and deterioration stepwise this should prompt clinicians away from ET. Although responses to alcohol, propranolol and a family history are sometimes evident, these are not reliable diagnostic features (5). The presence of other neurological signs, even if subtle or uncertain constitute the new entity **essential tremor plus (ET-plus)**(5) and warrant neurological input.

Essential tremor plus

Patients with ET-plus have ET features with additional signs that are subtle and their presence at times questionable. Dystonia is the most common of these and may include minimal flexion posturing of the fingers/wrist or pronation/supination tilting of the outstretched hands. This group either represent novel disorders or alternate conditions (dystonic tremor, PD) in their infancy. Although diagnostic value is currently lacking, practitioners are encouraged to attempt characterisations and consider referral as it could potentially alter future outcomes.

Enhanced physiological tremor (EPT)

EPT resembles ET and occurs due to an enhancement of normal physiology by precipitating conditions (anxiety, drugs and thyroid disease)(9). EPT tends to vary with these factors and not

functionally limit. The proposed 3-year ET observation period potentially aids in delineation and reversal of causes.

Tremor combined with parkinsonism

Classical parkinsonian tremor manifests with a 4-7 Hz asymmetrical hand, resting “pill-rolling” tremor with associated bradykinesia (with decrement) and rigidity. Lower limb, jaw, tongue or foot tremors can variably co-exist (5). Postural/kinetic (action) tremor resembling ET can be a presenting feature of PD. These patients should therefore be regularly re-examined for emergence of Parkinsonism. PD tremor usually abates with action or assuming a position with re-emergence with sustained posture (re-emergent tremor) (10).

Isolated focal tremors

Focal tremors affect the head, voice, palate or limbs and occur in isolated conditions or during specific tasks such as writing or while playing instruments or sport (11) (12)(13). These tremors potentially reflect underlying dystonia and should not be regarded as ET(5),(14). They can at times be attributed to an underlying lesion (14),(15) or suggest a genetic abnormality(16).

Isolated rest tremor without parkinsonism should either prompt careful clinical surveillance or imaging for dopaminergic deficiency(17). If rest tremor occurs in conjunction with an ET phenotype (typically in advanced stages) and in the absence of parkinsonism, this constitutes ET-plus (5).

Neurophysiological assessments can aid in distinguishing PD from ET rest tremor (18). Orthostatic tremor (OT) is an isolated tremor occurring mainly in patients’ lower limbs when standing. Although co-existent upper limb or head tremors can occur(19)(20) this should not be regarded ET. Diagnostic delays have been noted (19) as initial symptoms can be non-specific (legs feeling like jelly, unsteadiness). These features should therefore prompt a clinical suspicion for OT.

Dystonic tremor (DT) syndromes

If a tremor occurs in a body part affected by dystonia this is termed DT. Tremor and dystonia occurring in different body regions in contrast are defined as tremor associated with dystonia(5)(21). DTs are typically variable, and are jerky (21). Other distinguishing signs exist (21) though detection would not be expected in general practice. The distinction between DT and ET-plus with dystonia currently solely relies on the confidence of a clinician in apportioning dystonia though neurophysiology may change this in the future. Patients with DT can present with an isolated head tremor and/or associated head and neck posturing (cervical dystonia). This can occur in isolation or in combination with an asymmetrical upper limb tremor. DT's variable nature can sometimes lead to a misdiagnosis of a functional tremor. Specialist input should therefore be sought in these cases to firstly clarify the diagnosis but also for consideration of specific efficacious treatments such as botulinum toxin therapy or functional neurosurgery.

Intention tremor syndromes

Previously classified cerebellar tremor, these cases are now considered as either isolated or combined (typically dystonia or cerebellar signs) intention tremor syndromes. Intention tremors are typically <5Hz with an underlying cause in the brainstem-cerebello-thalamic pathway (5).

Functional Tremor

Functional tremor is diagnosed with the demonstration of 'positive' features (sudden onset and inconsistencies, fluctuations, distractibility and entrainability on examination). While a co-existing psychiatric history in particular anxiety can be present, it should not be relied upon(22).

Neurophysiology can sometimes aid the diagnosis (23) which should be established by a specialist.

3 'cardinal' questions clinical approach to tremor

A previously proposed approach of 3 'cardinal' questions to address neck pain could potentially be useful when considering tremor (6). The first consideration is if the complaint is an emergency though these presentations of tremor are rare. An abrupt onset and rapid progression (days to

weeks) is concerning. However, rapidly progressive tremor with other neurological features such as dysarthria, ataxia, seizures or a progressive gait and balance disorder warrants urgent neurological evaluation (24). This may relate to an acute toxic (drug induced) process or an immune mediated process. Immune mediated disorders can occur due to an underlying neoplasm, and result in significant long-term sequelae while early diagnostics and treatment can substantially alter outcomes (24). Toxic medication levels (e.g. lithium, valproic acid) are an alternate possibility. A thorough medication history, serum drug levels and an emergency admission should therefore be considered in cases with these features.

The next question is if further investigations or treatments are required in primary care. We propose that patients with isolated upper limb action tremor should have blood tests to exclude reversible causes (renal function, thyroid function). In young onset cases (<40) (all syndromes), Wilson's disease should be excluded with biochemical testing (liver function tests, serum ceruloplasmin and copper). In the absence of reversible causes and the presence of functional impairment, practitioners could consider initiating Propranolol or Primidone. In convincing PD cases with functional impairment trialling Levodopa may be worthwhile while awaiting specialist input, depending on local referral patterns and practice.

The final consideration is if the patient requires specialist input. We propose that all cases with a clinical syndrome rather than ET should be referred. This is to establish the diagnosis with certainty while facilitating specialised treatments (e.g. botulinum toxin and functional neurosurgery). ET cases refractory to medication with functional limitation would also benefit from specialist input for diagnostic validation and alternate treatment consideration. Functional neurosurgery for severe, refractory upper limb tremor and botulinum toxin treatment for head tremor may be very effective in selected cases.

Conclusion

We outline a clinical approach to upper limb tremor. The emphasis is to regard tremor as a symptom and to focus on defining a syndrome rather than presuming a diagnosis. This concept is particularly crucial when considering the common clinical syndrome of ET.

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