APPROACH TO THE SHAKY PATIENT

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Introduction to the Clinical and Diagnostic Approach to Tremor

A tremor is a rhythmic mechanical oscillation located in at least one body region. Tremor is defined by 1) the affected body region(s), 2) the condition during which tremor is activated (rest, posture, etc.), and 3) the frequency of the tremor. In general, a tremor less than 4 Hz is slow, 4-7 Hz is medium, and >7 Hz is fast.

In 1998, the International Parkinson and Movement Disorder Society (MDS) published a consensus statement on tremor. This paper defined tremor types by activating condition (1). The classification is as follows:

A. Rest tremor: This describes a tremor that occurs in a body part completely supported against gravity.

1. The limb is truly at rest and not voluntarily activated.
2. The amplitude of the tremor increases during mental tasks or with motor activation of another body part (i.e. hand tremor increases when walking).
3. The amplitude of the tremor diminishes or ceases during voluntary activities.

B. Action tremor: This describes a tremor that occurs during any voluntary activity. This is a broad category describing tremor that occurs during posture, intention, goal and non-goal directed activities.

1. Postural tremor: A tremor occurring when the limb is voluntarily held in a posture against gravity. A rare variant is when the tremor only occurs during a specific posture. This is identified as a position-specific or position-sensitive tremor.
2. Kinetic tremor: This describes tremor that occurs during any voluntary movement.
    a) Simple kinetic tremor: This occurs during non-goal directed movements and does not increase when approaching a target. It can be seen during movements such as flexion/extension of the wrist or pronation/supination of the hand.
    b) Task-specific kinetic tremor: This occurs during specific activities such as handwriting or playing a musical instrument.
    c) Intention tremor: This occurs during visually guided, goal directed activity. The tremor will enhance, increasing in amplitude as the limb approaches the target.
    d) Isometric tremor: This occurs when a voluntary muscle contraction is opposed by a rigid stationary object. It may be elicited by squeezing the hand into a fist or squeezing the examiner's fingers.

Physiologic and Enhanced Physiologic Tremor:

Physiologic tremor is present in neurologically healthy individuals. It is a low amplitude, high frequency postural tremor (2). Physiologic tremor can be subtle and may be missed during a routine physical examination. Slowing of the normal 8-12 Hz frequency should prompt a search for a pathological cause (e.g. essential tremor), irrespective of the patient's age (3, 4).

A physiologic tremor may become enhanced, and thus more visible. Emotions, muscle fatigue, medications, recreational drugs, alcohol, heavy metals, and medical conditions are all potential causes (5-13).
It is often unnecessary to treat an enhanced physiologic tremor. Addressing the underlying cause is the ideal way of treating the tremor. However, β-2 antagonists, such as propranolol, can be helpful for symptomatic tremor treatment when a reversible cause is not identified.

Tremor in Parkinson's disease (PD)

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease. Parkinson's disease typically presents after age 50, but can have a younger onset. The male to female ratio is 2-to-1 (14). The U.K. PDS Brain Bank Criteria (QSBB) is the most widely accepted validated clinical criteria for Parkinson Disease (https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/GetPdf.cgi?id=phd000042) (15, 16). According to the QSBB, the clinical diagnosis of PD requires the patient to have bradykinesia and at least one of the following clinical features: cogwheel rigidity, resting tremor or postural instability. Tremor is not required for the diagnosis of PD.

A. PD rest tremor: The rest tremor is a low frequency (4-6 Hz) tremor, which may have a "pill-rolling" appearance. Pronation-supination of the forearm or flexion-extension of the wrist may also be seen. At symptom onset, tremor is typically asymmetric. Tremor typically presents in an upper limb, although it can begin in other locations. Over time there is usually spread to the contralateral limb or the ipsilateral lower limb. Rest tremor may be present in the lips, jaw, or tongue; tremor in the voice and head is much less common (17). In PD patients, bradykinesia and rigidity often respond better to dopaminergic therapy than the rest tremor.
B. Postural (re-emergent) and kinetic tremor in PD: Postural tremor in PD usually emerges after a latent period following adaptation of a new posture. This is known as re-emergent tremor, and it can be the only visible tremor at presentation in these patients (18). Electrophysiological studies suggest that re-emergent tremor shares more pathophysiological mechanisms with the rest tremor of PD than with the postural tremor of essential tremor (19). Action tremor can also be present in PD; it often has a higher frequency and lower amplitude than the rest tremor.
C. Benign tremulous parkinsonism (BTP): The exact relationship between BTP and PD remains unclear. Patients who receive this controversial diagnosis have a prominent rest and action tremor, mild signs of parkinsonism, slow disease progression and a strong family history. Although it may be challenging to treat these patients with oral medications, they often have an excellent response to Deep Brain Stimulation (20-23).

The treatment of Parkinson's disease is complex. Young, tremor-predominant patients may be treated successfully with anticholinergic medications, like trihexyphenidyl or amantadine. Tolerance to anticholinergic medications decreases with age, and the tremor in older PD patients is often treated exclusively with dopaminergic agents. Low doses of clozapine may be tried in cases refractory to other medications (24). Deep brain stimulation often improves tremor. The most common target is the subthalamic nucleus, but the globus pallidus internus and rarely, the thalamus, have been successful targets as well (25-27).

Atypical Parkinsonism

In 2006, the AAN published practice parameters to guide clinicians trying to differentiate PD from atypical PD. (28) In 2013, the EFNS/MDS-ES made recommendations for the diagnosis of PD, including suggestions for differentiating PD from atypical PD (16). Although less frequent than in PD, tremor may appear in atypical parkinsonian conditions.

A. Vascular parkinsonism (VP): VP accounts for 2.5-5% of all cases of parkinsonism (29). Parkinson symptoms due to vascular disease may mimic "idiopathic" Parkinson's disease. Although there are no specific clinical features or diagnostic tests that can differentiate the two entities (30), [^{123}I]FP-CIT SPECT (DaTSCAN) may accurately differentiate between early Parkinson's disease and secondary parkinsonian conditions (31). Tremor is less common in VP than in PD. When tremor is present, postural tremor is more common than rest tremor. The most common presentation of VP is gait difficulty with symmetric involvement of the legs. Pseudobulbar palsy, dementia, freezing of gait, incontinence, early postural instability, and early falls are more common in VP than PD (29, 32, 33). Cognitive tests often demonstrate global dysfunction (34). Visual hallucinations are significantly less common in VP than in PD (35). MRI brain imaging is abnormal in 90-100% of VP compared to 12-43% of PD. Common abnormalities on imaging include multiple territory infarcts in the periventricular and subcortical white matter and basal ganglia infarctions (29, 30). Patients can respond to levodopa, although less frequently than in PD (29).

B. Lewy Body Dementia (LBD): Revised criteria for the diagnosis of LBD are available for reference (36). A reported 70% of patients have an akinetic-rigid syndrome (37). Patients with parkinsonism may have a rest tremor that is identical to that seen in Parkinson's disease. Most patients with tremor-predominant

LBD have a pill-rolling rest tremor “mixed” with action and postural tremor (30). Head tremor is more frequent in LBD vs PD, present in up to a 25% of patients with LBD compared to 3% of patients with PD (38). Over 50% of patients with LBD develop tremor in the legs upon standing compared to less than 5% of PD patients. Upon walking, leg tremor terminates (38). A diffusion of tremor throughout the body, or “overflow” tremor may be observed in LBD patients when patients are asked to stand with their arms outstretched. Spread of tremor has latency up to 15 seconds for hand tremor and up to 30 seconds for leg tremor. This finding was observed in 46.6% of LBD vs. 3.1% of PD patients, < .001 (38). Tremor in LBD patients should be distinguished from myoclonus, which happens frequently in these patients (39).

C. Progressive supranuclear palsy (PSP): PSP is a tauopathy with many phenotypes, and variable response to levodopa. It is commonly characterized by parkinsonism (with prominent gait and balance disturbance), supranuclear ophthalmoplegia, pseudobulbar palsy, and prominent neck dystonia. Although tremor is less common in PSP when compared to PD (40), a review of 103 pathologically-confirmed cases reported tremor in 20% of PSP patients (41). In a more recent study of 344 PSP cases who underwent a standard neuropathological assessment, immunohistochemical evaluation for tau and α-synuclein, and DNA genotyping for the MAPT H1/H2 haplotype, 146 (42%) presented some form of tremor, including including postural/action tremors, resting tremor, intention tremor, or a combination of different types of tremor (40).

D. Multiple systems atrophy (MSA): MSA is a heterogeneous disorder featuring parkinsonism, a variable response to levodopa and rapid disease progression (42). Other symptoms include dysautonomia, urinary impairments and orthostatic hypotension (43). Two phenotypes are described: the parkinsonian variant (MSA-P) and the cerebellar variant (MSA-C), which can feature axial and appendicular ataxia (44). The pathologic hallmark of MSA includes glial cytoplasmic inclusions and the absence of Lewy bodies. Up to 80% of MSA patients will exhibit a tremor, and patients MSA-P are more commonly affected. About 50% of MSA patients will have a jerky postural tremor, with evidence of polyminimyoclonus on electrophysiology. Resting tremor has been reported in over 30% of patients, but only about 10% have a typical PD rest tremor (42).

E. Corticobasal degeneration (CBD): Corticobasal degeneration is a pathologic diagnosis that has four proposed phenotypes: (a) corticobasal syndrome (CBS), (b) frontal behavioral-spatial syndrome (FBS), (c) nonfluent/agrammatic variant of primary progressive aphasia (naPPA), and (d) progressive supranuclear palsy syndrome (PSPS). Clinical criteria for CBS are available for reference (45, 46). Few patients will meet full criteria for CBS in the first two years of the disease course (47). Levodopa therapy may produce mild to moderate clinical response, which is typically transient. Tremor occurs in less than 40% of patients over the entire disease course (only 20% at the time of presentation), and has a varying phenotype that includes tremor at rest, posture, and action. A classic 4-6 Hz rest tremor is uncommon. Low-amplitude action myoclonus can mimic tremor, and has been reported in over 40% of cases (46, 48). Myoclonus is often stimulus sensitive, and may be responsive to benzodiazepines or levetiracetam. (45, 49).

F. Normal pressure hydrocephalus (NPH): Normal pressure hydrocephalus (NPH) is commonly identified by the subacute, insidious onset of the clinical triad of gait disturbance, cognitive impairment and urinary urgency or incontinence (50). Gait is often an early and disabling feature. The gait of both Parkinson’s and NPH patients may exhibit slowness, small steps, and balance difficulties (51). Unlike the narrow-based Parkinson stance, the stance in patients with NPH is broad based (52). Patients with NPH may have a gait described as “magnetic”; this refers to the feet appearing stuck to the floor as the patient attempts to walk. Gait initiation is difficult and patients often turn en bloc. As an alternative to a formal screen, impairments in at least two of the following should be seen: psychomotor slowing, decreased fine motor speed, impaired attention, impaired recall-especially for recent events, behavioral changes, or executive dysfunction (53). Rest tremor is not a common feature of normal pressure hydrocephalus but can be present and respond to ventriculoperitoneal shunting (54, 55).

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