Neurology: Differential Diagnosis of Tremor

Rigor, tremor, akinesia: The classic triad of symptoms of Parkinson's disease, which you can probably recite in your sleep. However, a tremor is also a symptom of several other disorders that are relevant in clinical practice. In the following article we discuss the most important differential diagnosis of tremor. By studying the many examples and tips in this article you will be perfectly prepared for clinical exams.

Tremor: At a Glance

In this article we discuss the following forms of tremor. The ones, which are particularly relevant for exams are highlighted.

- Physiologic tremor
- Rest tremor
- Essential tremor
- Dystonic tremor
- Intention tremor/cerebellar Tremor
- Orthostatic tremor
- Rubral tremor/Holmes-Tremor
- Neuropathic tremor
- Psychogenic tremor
- Wilson disease
Definition of tremor

**Tremor**: lat. tremere = shaking, trembling

Tremors are defined as involuntary, oscillatory and rhythmic muscle contractions of a body part at a relatively constant rate. Alternate contractions in agonist and antagonist muscles lead to tremor. The tremor is the most common form of all movement disorders.

Diverse causes of tremor

<table>
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<th>TREMOR</th>
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<td>Essential Neurological diseases</td>
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<tr>
<td>Multiple sclerosis, Parkinson's disease, cerebellar disorders</td>
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Based on its pathophysiology tremor is classified as an extrapyramidal disease and abnormal movement disorder, typically involving not only the hands but also for example the head, trunk, and the voice, either individually or in different combinations.

The most common tremor seen in primary care is enhanced physiologic tremor, which is followed by essential tremor and the tremor of Parkinsonism. All tremors present more commonly in the old age.

Tremor assessment criteria

The two tremor assessment criteria are:

- Tremor frequency
- Situation of occurrence

Classification and characteristics of the 3 most important forms of tremor

<table>
<thead>
<tr>
<th>Type of tremor</th>
<th>Description</th>
<th>Frequency</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting tremor</td>
<td>Occurs in a body part that is relaxed and completely supported against gravity.</td>
<td>4-6 Hz</td>
<td>Parkinson's disease</td>
</tr>
<tr>
<td>Postural tremor</td>
<td>Occurs when holding a position against gravity, such as holding your arm or leg outstretched.</td>
<td>4-8 Hz</td>
<td>Essential tremor</td>
</tr>
<tr>
<td>Action tremor</td>
<td>Only occurs when voluntary movements are attempted. This type of tremor also includes the Intention tremor, which occurs specifically during voluntary movement towards a target.</td>
<td>2-4 Hz</td>
<td>Cerebellar damage, essential tremor, primary writing tremor</td>
</tr>
</tbody>
</table>


**Study tip**: Read the case studies well - the questions in your exams on the various forms of tremor are frequently linked to the typical clinical symptoms mentioned in an introductory case study given below, before the topic.
Physiological Tremor

**Physiological tremor** is an action tremor and is present in every healthy person when muscles are activated. Physiological tremor is characterised by a high frequency and a low amplitude of typically **8-13 Hz**. This type of tremor occurs in all people, in particular in the presence of stressors, for example psychomotor agitation stressful situations, during exams and when it is cold. The **enhanced physiological tremor** (drug-induced and toxic tremor) occurs as a side effect or sign of withdrawal from certain drugs.

A long list of medications can exacerbate tremors. Medicines most commonly implicated are sympathomimetics, (amphetamines, terbutaline, and pseudoephedrine), psychoactive medications (e.g., tricyclic antidepressants, haloperidol, and fluoxetine, lithium, valproic acid). Similarly, a large number of metabolic disorders can cause tremor. The most common ones are hepatic encephalopathy, hypocalcemia, hypoglycemia, hyponatremia, hypomagnesemia, hyperthyroidism, hyperparathyroidism, and vitamin B12 deficiency.

Alcohol withdrawal can also cause enhanced physiologic tremor.

Rest Tremor

**Image:** “Sir William Richard Gowers, neurologist, researcher and artist, drew this illustration in 1886 as part of his documentation of Parkinson’s Disease. The image appeared in his book, A Manual of Diseases of the Nervous System, still used today by medical professionals as a primary reference for this disease.”

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**Case study:** For some time, a 65-year-old man has noticed a progressive slowing of his movements. When walking his steps have become smaller and he has developed a forward-flexed posture. He has difficulty getting up from deep armchairs and turning over in bed at night. His handwriting has become smaller. Additionally, the patient presents with a slight resting tremor, which is more pronounced in the right hand than it is in the left. Furthermore, the patient suffers from significant back pain. […] via M. Wehling: Clinical Pharmacology. Thieme Publishers 2011
Diagnosis of resting tremor

If a patient as in this case presents with resting tremor affecting one side you have to primarily consider Parkinson’s disease as the cause. To confirm this tentative diagnosis look for the other two cardinal symptoms characteristic for Parkinson’s disease, rigor and hypokinesia. An altered posture and decreased facial expressions usually occur early in Parkinson’s disease and relatives are typically the first to notice these changes. Additional symptoms that may indicate an atypical Parkinson’s disease must be excluded. Parkinson’s tremor may be continuous or intermittent with fluctuating frequency and amplitude and increases with mental stress.

Parkinson’s disease characteristic cogwheel rigidity may be the result of tremor and increased muscle tone (rigor). In Parkinson’s disease frequency of rest tremor is at 4-6 Hz and because of that it is also called ‘pill-turning tremor’. More than 70 percent of patients with Parkinson disease report tremor.

The tremor can become bilateral after several years, but the limbs do not tremble in synchrony.

Treatment of the parkinsonian resting tremor

Everything on the treatment of Parkinson’s disease can be found here.

Essential Tremor

Case study: A 66-year-old woman is the carer for her considerably older husband. For some time she has observed a tremor in her hands. Also her father had suffered from this in old age. However, she feels safe when climbing stairs or walking, and also does not suffer from dizziness. The hand tremor occurs especially when she for example wants to pour tea into a cup or wants to carry out other focused activities. In emotionally stressful situations the tremor also enhances.

The essential tremor is, as described in this case, an action and postural tremor and is at the frequency of 4-8 Hz slightly below the frequency of the physiological tremor. The essential tremor occurs with no apparent neurological underlying disease. The psychological strain is high in patients with essential tremor as people with trembling or shaking hands are often wrongly judged or labelled as alcoholics.

Epidemiology of essential tremor

Essential tremor is the most common form of tremor (5 % of the population are affected).

The essential tremor may occur at any age, but most often in early adulthood. But many patients seek help for it only after old age sets in because of its progressive nature. Men and women are equally affected.

Clinic and diagnostics of the essential tremor

In patients with a positive family history, the essential tremor is called familial tremor. The mode of inheritance is mostly autosomal-dominant. Unlike the resting tremor, the essential tremor usually begins symmetrically in both arms and can affect the head and larynx area. Depending on which muscles are affected, this can result in a no-no tremor (shaking of the head) or a yes-yes tremor (nodding of the head). If the vocal
cords are affected, patients suffer from a shaking or quivering sound to the voice. Tremor involves multiple body parts in majority of cases (~50%), followed by head in ~30% of cases, voice in ~20%, tongue in ~20%, face/jaw in ~10%, and lower limbs in ~10% of the cases. The tremor is improves on consuming alcohol and worsens in times of stress.

Essential tremor treatment

Pharmacological treatment includes cardioselective beta blockers such as propranolol, antiepileptic drugs such as primidone, gabapentin and topiramate or botulinum toxin type A. Patients with medication-resistant tremor may benefit from deep brain stimulation of the ventral intermediate thalamic nucleus (VIM) instead.

Image: "Parkinson Surgery" by Thomasbg. License: CC BY-SA 3.0
Intention Tremor in Cerebellar Diseases

Case study: A 21-year-old previously healthy woman consults her physician. For a few days she has experienced a slight tremor in her right hand, which increases when she carries out a deliberate target-directed movement. As she does not present with any other symptoms and has a busy professional and personal life, her GP, for the time being, suggests further observation of her symptoms [...] via J. Priewe et al.: Das Erste. Springer Publishing 2007.

Definition of intention tremor

Intention tremor (also ataxic tremor/cerebellar tremor) is a subtype of the action tremor. This tremor is characterised by trembling of the limbs during a voluntary targeted-directed movement. The Intention tremor is caused by lesions in or damage to the cerebellum. The intention tremor does not occur during periods of rest. The intention tremor affects the trunk and the extremities and can occur either unilateral or bilateral.

Etiology of intention tremor

The intention tremor is symptomatic and a clinical sign of cerebellar disease. Cerebellar lesions will result in a lack of coordination of ongoing movements (ataxia).

Causes of cerebellar tremor may be:

- Tumours
- Haemorrhage
- Ischaemic strokes
- Inflammatory lesions, characteristic in multiple sclerosis (in the case study, the patient’s intention tremor is the first clinical manifestation of multiple sclerosis). One of the commonest causes of intention tremor is multiple sclerosis.

Diagnosis and treatment of intention tremor

Intention tremor has the lowest frequency at 2-4 Hz. A pathologic finger-nose test is indicative of an intention tremor. Frequently, difficulty executing fine motor movements can be observed for example if the affected person is asked to grasp an object with both hands. Dysmetria i.e. overshoot on finger-to-nose testing, dyssynergia i.e. abnormal heel-to-shin testing, atraxia, and hypotonia is suggestive of a cerebellar lesion.

Drugs such as topiramate, clonazepam or propranolol are used to treat intention tremors in off-label use. In case of unsatisfactorily results, a deep brain stimulation of the ventral intermediate thalamic nucleus (VIM) may be considered.

Dystonic Tremor

Definition of dystonic tremor

Dystonic tremor is predominantly a postural and kinetic tremor in muscles affected by dystonia. The frequency of dystonic tremor is 3-7 Hz. Typical examples are the dystonic head tremor, the dystonic writing tremor or the dystonic vocal tremor. The exact
cause of dystonia is unknown. Some forms of dystonia are genetic, while others are secondary (acquired). It is typically seen in patients younger than 50 years. Its frequency and amplitude are often irregular.

Clinical manifestation and treatment of dystonic tremor

Patients with dystonic head tremor often present with an abnormal head posture (torticollis). Dystonic tremors affecting the hands gets frequently confused with resting tremors characteristic for Parkinson’s disease. In many patients with dystonic tremor gestes antagoniste lead to a reduction in tremor amplitude (and improvement of the dystonia). Treatment of the tremor is followed by the treatment of dystonia. The most common treatment involves drugs such as botulinum toxin, anticholinergics and tiapride. In case of resistance to treatment, a deep brain stimulation may be considered.

Orthostatic Tremor

Orthostatic tremor is a high-frequency tremor which usually is not visible on the outside. The cardinal symptom of orthostatic tremor is a sense of unsteadiness on standing. Primary causes of orthostatic tremor are unknown. Orthostatic tremor also occurs secondary to some disorders like for example in Parkinson’s disease.

Clinic, diagnostic and therapy of orthostatic tremor

Orthostatic tremor is characterised by a particularly high frequency of 16 Hz, affecting predominantly the legs. Patients complain about a feeling of swaying and sense of unsteadiness on standing. These symptoms often improve as the patient starts to walk. Patients often describe a typical unsteady feeling in the legs which may even lead to falls.

Note: In patients with orthostatic tremor the symptoms resolve when the affected person is walking, sitting, or lying down. Diagnosis is usually obtained based on clinical evaluation combined with surface electromyogram (EMG). Confirmation of the diagnosis can be obtained by EMG showing such high frequency patterns.
For the treatment of orthostatic tremor, drugs like gabapentin or clonazepam are used. In very severe cases, deep brain stimulation of the ventral intermediate thalamic nucleus (VIM) may be considered.

### Holmes’ Tremor: Rubral Tremor in Brainstem Lesions

#### Definition of Holmes’ tremor

Clinically, Holmes’ tremor is defined as a **combination of symptomatic rest, action and postural tremors**. Holmes’ tremor is caused by lesions affecting the brainstem, cerebellum and thalamus. Brainstem stroke, trauma, vascular malformations and inflammatory lesions characteristic for multiple sclerosis are the most common causes for Holmes’ tremor.

#### Clinical manifestation and treatment of the Holmes’ tremor

Holmes’ tremor tends to have a slightly lower frequency than the Parkinson’s tremor: **3-5 Hz**.

The majority of cases of Holmes’ tremor do not respond to pharmacological treatment. Similar to the treatment of cerebellar tremor the Holmes’ tremor can also be treated using medications like L-dopa and dopamine agonists, anticholinergics, clonazepam or clozapine, off-label. Again, thalamic deep brain stimulation of the ventral intermediate thalamic nucleus (VIM) may be considered.

### Neuropathic Tremor

#### Definition of neuropathic tremor

Neuropathic tremor is a centrally generated tremor. This form of tremor often occurs in peripheral neuropathies, for example in **demyelinating neuropathy**. However, the severity of the tremor does not correlate with the severity of the neuropathy. Frequently, patients are affected who suffer from demyelinating hereditary motor and sensory neuropathies (HMSN), or patients with inflammatory neuropathies (e.g. CIDP).

#### Clinical presentation and treatment of the neuropathic tremor

In addition to neuropathic pain, patients suffer from a high amplitude tremor of **4-8 Hz** frequency.

Treatment of the underlying inflammatory neuropathy usually improves the neuropathic tremor. In addition, medical treatment with propranolol, primidone or pregabalin may be considered. According to case reports, a deep brain stimulation of the ventral intermediate thalamic nucleus (VIM) can provide remarkable therapeutic benefits.
Psychogenic Tremor

A Psychogenic tremor can present with features like abrupt onset, spontaneous remission, changing tremor characteristics, extinction with distraction, and h/o associated stressful life event.

Wilson disease

Wilson disease, an autosomal recessive disorder, can manifests in young persons with a “wing-beating” tremor.

Overview: Treatment of the Most Common Forms of Tremor

<table>
<thead>
<tr>
<th>Tremor</th>
<th>1. Choice of medication</th>
<th>Surgical approach (if pharmacological treatment is insufficient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s tremor</td>
<td>Dopamine agonist drugs</td>
<td>Deep brain stimulation (mainly nucleus subthalamus, exception VIM)</td>
</tr>
<tr>
<td>Essential tremor</td>
<td>Propranolol, primidone</td>
<td>Deep brain stimulation (VIM)</td>
</tr>
<tr>
<td>Cerebellar tremor (intention tremor)</td>
<td>Limited success with ondansetron, carbamazepine</td>
<td>Treatment success in selected patients: Deep brain stimulation (VIM)</td>
</tr>
<tr>
<td>Dystonic tremor</td>
<td>Local botulinum toxin injections, anticholinergic drugs</td>
<td>Deep brain stimulation (VIM) may be considered in patients not responding to drug therapy</td>
</tr>
<tr>
<td>Enhanced physiological tremor</td>
<td>Treatment depends on accurate diagnostic evaluation of the cause</td>
<td></td>
</tr>
<tr>
<td>Orthostatic tremor</td>
<td>Gabapentin, clonazepam</td>
<td>In severe cases: Deep brain stimulation surgery (VIM)</td>
</tr>
</tbody>
</table>

Note: VIM = ventral intermediate thalamic nucleus  (Source via Ärzteblatt 13/2014)

Approach to Diagnosis of Tremor:

The following questions should be asked when evaluating a patient with tremor:

1. Is tremor enhanced physiologic?
2. H/o using medications that can induce tremor?
3. Is tremor relieved with distraction?
4. Age group: young or old?
5. Young: Copper levels? Multiple anatomic/genetic/metabolic issues?
6. Old: Rest, Postural or action? H/o Alcoholism?
7. Head imaging (MRI)?
8. Propanolol trial?

Popular Exam Questions in Neurology: Differential Diagnosis of Tremor

The answers are below the references.

1. The essential tremor is an action and postural tremor. Which of the following statements on the essential tremor is not true?

A. Essential tremor frequency ranges between 4-8 Hz.
B. The essential tremor is also called the pill-rolling tremor.
C. The essential tremor typically improves after alcohol consumption.
D. A positive familial anamnesis can be found frequently in patients diagnosed with essential tremor.
E. The essential tremor usually begins symmetrically in both arms.

2. A 63-year-old patient suffers from depressive mood swings for two and a half years. She has experienced increasing pain in both shoulder joints and along the spine. Writing causes her difficulty, even her typeface has changed: The letters have become significantly smaller. When she gets upset, she feels a tremor in her right hand. Which diagnosis most likely applies in this case?

A. Alzheimer's disease
B. Essential tremor
C. Idiopathic Parkinson's disease
D. Multiple sclerosis
E. Dementia with Lewy bodies

3. A 65-year-old to date healthy patient presents in your surgery. He has noticed a tremor in his right hand within the last six months, which has continually increased. If he experiences a stressful situation, the tremor further intensifies. If his hand simply lays in his lap, the tremor is particularly strong. If he carries out active movements on the other hand, the tremor improves. On clinical examination the medical history of the patient is confirmed.

A. Resting tremor in Parkinson's disease
B. Orthostatic tremor
C. Holmes tremor
D. Essential tremor
E. Cerebellar tremor

References
Bender et al.: mediscript Kurzlehrbuch Neurologie. Elsevier Verlag 2013
Differenzialdiagnose und Therapie des Tremors (2014) via Ärzteblatt

Correct answers: 1B, 2C, 3A

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