# MYOCLONUS VIDEO DIAGNOSIS AND TREATMENT

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Myoclonus is a brief, sudden, shock- or lightning-like jerky movement. It is considered to be the hyperkinetic movement disorder phenomenology with highest velocity.

**How to differentiate myoclonus from other phenomenologies?**
The key feature of myoclonus is very brief duration of the jerk, in line with its less than 200 millieseconds of the burst duration on electrophysiologic studies. While dystonia can have a jerky quality, dystonic jerks are not as brief as in myoclonus, and often associated with abnormal posturing. It may not be difficult to differentiate chorea from myoclonus, since the quality is different from jerks. Tics can have a jerky quality but the duration is not as brief as in myoclonus, and are usually associated with premonitory urge and suppressibility.

Myoclonus with small fine amplitude usually in fingers, called "*minipolymyoclonus*", can sometimes be confused with tremor. One helpful distinguishing feature is its jerky quality, as opposed to oscillatory sinusoidal quality of the tremor. Most myoclonic jerks are often worse or more prominent with action, for example, when holding arms up or reaching a hand out to touch an examiner's finger or object. Thus, sometimes patients with "*cortical tremor*", a form of cortical myoclonus, can be misdiagnosed as "essential tremor". This particular form of myoclonus is typically seen in familial cortical myoclonic tremor with epilepsy (FCMTE). Clinicians should observe carefully to identify jerky quality or irregularity when present.

In contrast, some forms of myoclonus may appear oscillatory, tremor-like, rather than jerky such as *palatal myoclonus* (hence called "palatal tremor" by some, but indeed confirmed to be myoclonus electrophysiologically). Jerks may not be as brief in some forms of myoclonus, correlating with their longer burst of duration, such as in *spinal segmental or propriospinal myoclonus*. *Hemifacial spasm*, a form of peripheral myoclonus, can even have a tonic quality (resembling dystonia), in addition to its phasic or jerky quality in some patients. Pattern recognition is very helpful in identification of these forms of myoclonus.

**Phenomenologic description of myoclonus**
When clinicians encounter a patient with myoclonus, attention should be paid to these phenomenologic characteristics before proceeding to the next steps in diagnostic approach.

1. Distribution: body regions (e.g. axial vs. limbs), what part of the limb (e.g. proximal vs. distal). This can be described further into focal, segmental (involving contiguous body regions), multifocal or generalized.

2. Positive vs. negative myoclonus. Most myoclonic jerks including in the definition above are positive myoclonus. However, myoclonus can be negative, due to lapse of postural tone such as asterixis (or its misnomer "flapping tremor") which can be seen in different conditions, not specific only to hepatic or uremic encephalopathy.

3. Amplitude: low or high amplitude. For examples, cortical myoclonus tends to have low amplitude (and involve distal limbs or fingers).

4. Rhymicity and consistency: rhythmic or non-rhythmic; intermittent (frequent vs. infrequent) or constant/continuous (e.g. in epilepsia partialis continua). Examples of rhythmic myoclonus include epilepsia partialis continua and palatal myoclonus.

5. Myoclonus occurs at rest or with action: Most myoclonic jerks are more prominent with action. Is there any specific task that brings out myoclonus such as pouring water or writing (e.g. in myoclonus-dystonia syndrome or DYT11 dystonia, but also in other forms)?

6. Synchronicity: synchronous vs. asynchronous. For example, in posthypoxic myoclonus or hyperekplexia, both sides of the arms and/or legs may jerk synchronously.

7. Stimulus sensitivity: It is important to examine myoclonus with different stimuli such as tactile (by using safety pin to touch a finger), auditory or visual stimuli. However, if jerks occur frequently, it may be difficult to determine stimulus sensitivity.

8. Associated neurologic or systemic features: For example, other movement disorder phenomenologies (dystonia, ataxia, etc.), eye movement abnormalities (e.g. opsoclonus, pendular nystagmus, oculomotor apraxia, vertical supranuclear gaze palsy, etc.) and focal findings on neurologic examination can be very helpful clues to the diagnosis.

**How to approach myoclonus in the clinic?**
In other phenomenologies such as chorea, dystonia or parkinsonism, the conventional neurological approach of "anatomical localization" may not be very useful (since most of them are basal ganglia in origin) except in rare circumstances (such as hemichorea or hemidystonia). In contrast, in myoclonus, anatomical localization plays a crucial role in both diagnostic approach and treatment guidance.

After characterizing the phenomenology of myoclonus, we follow these two main questions:

1. What is the anatomical localization of myoclonus? Cortical vs. subcortical/brainstem vs. spinal vs. peripheral?

2. Given the previously determined localization, what is the diagnosis? In this step, *associated neurologic and systemic features* will be very helpful clues. Some forms of myoclonus may easily be diagnosed by pattern recognition e.g. palatal myoclonus or hemifacial spasm.

**Myoclonus based on anatomical localization**
In order to be able to answer two main questions above, the knowledge of phenomenologic characteristics of myoclonus based on anatomical localization is important. We will also select some important differential diagnoses in each location to discuss in more detail.

**I. Cortical myoclonus**

General phenomenologic features
Cortical myoclonus typically involves distal limbs, especially hands or fingers, given their large area of homuncular representation. The amplitude of cortical myoclonus is generally small or fine, but may vary. It is usually worse with action, but can present at rest, either from the onset or when severity of myoclonus progresses. Cortical myoclonus is often sensitive to tactile stimuli with relatively short latency between the stimulus and reflex myoclonus due to fast-conducting corticospinal pathways, as opposed to longer latency in propriospinal myoclonus (see below). For example, when a patient has small amplitude of myoclonic jerks at his fingers, we examine by touching a myoclonic finger with a safety pin. If the patient has stimulus sensitivity, a myoclonic jerk very briefly after the tactile stimulus will be demonstrated.

Electrophysiologic studies including back-averaged electroencephalography (EEG) and multi-channel surface electromyography (or poly-EMG) play an important role in understanding of myoclonus, both in clinical and research settings. However, most physicians do not have access to these studies. So clinical characterization remains very important. Detailed discussion about electrophysiology of myoclonus is beyond the scope of our clinical review. Briefly, electrophysiologic signatures of cortical myoclonus include spikes or sharp waves shortly preceding the jerks on back-averaged EEG, giant somatosensory-evoked potentials (giant SEP), enhanced C-reflex, and fast rostrocaudal recruitment (spreading pattern; not the same meaning as motor recruitment in conventional EMG studies). Due to the presence of preceding sharp waves, some have viewed cortical myoclonus as a forme fruste of myoclonic epilepsies. In fact, epilepsia partialis continua is also a form of cortical myoclonus.

Differential diagnoses of cortical myoclonus
The differential diagnoses of cortical myoclonus are very broad, compared to the other anatomical location. These include **epileptic** (e.g. progressive myoclonic epilepsies, epilepsia partialis continua), and **secondary/symptomatic** (e.g. from heredodegenerative disorders, vascular insults, drug-induced, infectious-related such as subacute sclerosing panencephalitis [SSPE] or prion disease, and metabolic causes).

Probably one of the most common causes of cortical myoclonus in general medical practice is due to metabolic encephalopathies such as uremic or hepatic encephalopathy. Clinical pearls of some selected disorders presenting with cortical myoclonus are summarized in Table 1.

**Table 1.** Selected important myoclonic disorders categorized by anatomical localization

| Disorders | Clinical pearls |
|---|---|
| **Cortical myoclonus (selected disorders)** | |
| Epilepsia partialis continua | • Often involves face and an upper extremity<br>• Involvement of masseter can help differentiate from hemifacial spasm<br>• May be associated Rasmussen's encephalitis (where immunotherapies may be helpful) and focal cortical lesions |
| Progressive myoclonic epilepsies | • Also previously called "progressive myoclonic ataxia" or "Ramsay-Hunt syndrome"<br>• DDx includes Unverricht-Lundborg disease (EPM1 encoding cystatin B), Lafora body disease (EPM2A or EPM2B encoding laforin), neuronal ceroid lipofuscinosis (or Batten disease), sialidosis and myoclonic epilepsy with ragged-red fibers (MERRF) |
| Posthypoxic myoclonus (or Lance-Adams syndrome) | • Acute and chronic forms<br>• Some may also contribute to brainstem localization (including in a form of "reticular reflex myoclonus")<br>• Occurs after respiratory arrest (only cardiac arrest is NOT sufficient)<br>• Positive or negative myoclonus<br>• Limbs +/- axial involvement, multifocal or generalized<br>• Acute form is often synchronous and responsive to auditory and/or tactile stimuli<br>• Action component typically impairs daily functions<br>• Classic "bouncing" gait due to negative myoclonus when standing<br>• One of alcohol-responsive movement disorders (see Table 3) |
| Myoclonus associated with neurodegenerative disorders | • Myoclonus can be seen in various dementia syndromes such as Alzheimer's disease, frontotemporal dementia, and parkinsonian disorders especially corticobasal syndrome (typically asymmetric involvement in unilateral arm), multiple system atrophy (minipolymyoclonus or myoclonus in lower cranial region), but also, less prominently, in Parkinson's disease |
| Cortical tremor (familial cortical tremor with myoclonic epilepsy) | • Onset in adults<br>• May resemble "essential tremor" but the clue is jerky quality of "tremor"<br>• Family history and/or seizure may be absent<br>• Multiple different names exist (e.g. benign adult familial myoclonic epilepsy) |
| **Subcortical and brainstem myoclonus** | |
| ***Subcortical myoclonus*** | • Myoclonus in myoclonus-dystonia syndrome (see dystonia lecture) and orthostatic myoclonus have been proposed to originate from subcortical origin<br>• However, exact mechanisms or localization remain unclear<br>• Orthostatic myoclonus may mimic orthostatic tremor clinically and generally requires electrophysiologic study to differentiate |
| ***Brainstem myoclonus*** | |
| ➢ Hyperekplexia | • Exaggerated startle<br>• Myoclonic jerks typically occur after auditory stimuli or tactile stimuli at the mantle (forehead and bridge of nose) area<br>• Can result in stiffness<br>• Genotypic variability; associated with multiple genes and several different inheritance (AD, AR and rarely X-linked forms), mostly encoding presynaptic and postsynaptic proteins in brainstem glycinergic neurons<br>• Anatomical target is at nucleus reticular gigantocellularis |
| ➢ Palatal myoclonus (PM) | • Slow 2 Hz "oscillation" of soft palate. Called "palatal tremor" by some (but indeed myoclonus electrophysiologically).<br>• Two forms:<br>1. Essential PM - no lesions seen on MRI, no ear click, tensor veli palatini involvement<br>2. Symptomatic PM - due to lesions e.g. stroke (delayed complication - several months after), demyelination in Guillain-Mollaret triangle, or Whipple's disease: may see inferior olivary hypertrophy; associated with ear click, pendular nystagmus, levator veli palatini involvement (although difficult to differentiate from tensor veli palatini clinically)<br>• Patients with "progressive ataxia with palatal tremor (PAPT)" have been found to have adult Alexander's disease (classic "tadpole" sign due to spinal cord atrophy on MRI) |
| ➢ Opsoclonus-myoclonus ataxia syndrome (OMAS) | • May not have all three features of opsoclonus, myoclonus and ataxia<br>• Oscillopsia if ocular flutter (bursts of back-to-back saccades only in horizontal phase) or opsoclonus (in multiple trajectories) present.<br>• Important to do CSF examination and neuroimaging of brainstem to rule out structural lesion in brainstem, postinfectious and paraneoplastic process<br>• In some of young children, associated with anti-Ri syndrome or neuroblastoma |
| ➢ Progressive encephalomyelitis with rigidity and myoclonus (PERM) | • Autoimmune process<br>• Associated with anti-glycine receptor in some patients<br>• Myoclonus originates from brainstem but often spread<br>• Often associated with stiffness syndrome<br>• Important to rule out brainstem structural lesion and encephalitis, and not to miss due to response to immunotherapies |
| **Spinal myoclonus** | |
| Spinal segmental myoclonus | • Myoclonic jerks in myotome corresponding to spinal lesion<br>• Requires neuroimaging to search for structural lesion |
| Propriospinal myoclonus (PSM) | • Axial jerks, typically truncal flexion (of note, another form of myoclonus that can cause axial jerks especially in cervical area is reticular reflex myoclonus)<br>• Long latency of reflex myoclonus after tactile stimulation due to possibly slow-conducting propriospinal pathway (yet not fully proved in humans)<br>• Psychogenic PSM has been reported based on presence of Bereitschaftspotential (signature of voluntary movement)<br>• However, some studies reveal microstructural abnormalities (disruption of white matter tracts on DTI) in some cases |
| **Peripheral myoclonus** | |
| Hemifacial spasm | • May look jerky (phasic form) or more sustained (tonic form) or mixed<br>• Patients may not have clear history of facial nerve lesion or Bell's palsy, but synkinesis are usually present<br>• Typically has gradient of involvement: upper or lower eyelid at onset, more prominent at upper than lower facial regions<br>• Worse when speaking (thus patients tend not to speak, in contrast to blepharospasm)<br>• May have elevation of the eyebrow on affected side (Babinski-2 sign)<br>• Requires MRI with thin-cut around facial nerve level to rule out compressive structural lesion, but uncommonly found<br>• BoNT is a treatment of choice. We generally do not send patients for microvascular decompression |
| Myoclonus due to focal peripheral (nerve root, plexus or peripheral nerve) lesions | • Involved muscles corresponds to dermatome, plexus or peripheral nerve distribution<br>• Requires neuroimaging (spinal cord, plexus) and/or EMG |

## II. Subcortical myoclonus and brainstem myoclonus

General phenomenologic features

Examples of **subcortically-generated myoclonus** (excluding brainstem myoclonus) **include myoclonus-dystonia syndrome and orthostatic myoclonus**. The origins of these entities have been proposed to be subcortical, but the exact location remains unknown. Myoclonus-dystonia syndrome was previously classified as "essential myoclonus", but has now known to be genetic, designated as DYT11 (*SGCE* mutations), and also DYT15 (unknown gene), and DYT26 (*KCTD17* gene). Please refer to our dystonia syllabus for more detail regarding this entity.

Orthostatic myoclonus has clinical features similar to orthostatic tremor. Patients typically present with imbalance or instability when standing which improves when walking or sitting. Leg shaking is low in amplitude, so is often not recognized by patients or examiners. "Helicopter sign" may be appreciated when putting stethoscope on a patient's thigh when standing. Later it has been found on electrophysiologic studies that some cases of "orthostatic tremor" indeed had orthostatic myoclonus. However, clinically it is probably impossible to differentiate between these two. Clinical implications of distinguishing between them remain unclear and treatment may be overlapping (e.g. levetiracetam).

Brainstem myoclonus typically involves cranial muscles which have innervation from brainstem motor nuclei, especially V, VII, IX, X, XI, XII-innervated muscles. Lower facial and neck muscles are often involved. This predilection of involvement, along with what seen in branchial and palatal myoclonus may suggest some relationship between myoclonus in this region and branchial arches during embryological development. Myoclonus can spread, usually down, to other contiguous regions such as cervical paraspinal muscles, proximal arm muscles or even further down to the entire body including limbs such as in hyperekplexia.

Myoclonus originates from brainstem tends to have sensitivity to auditory or tactile stimuli. The classic example of this is **hyperekplexia** in which jerks appear after clapping or touching mantle area of the face (T-zone between eyebrows and bridge of nose). However, we discourage repetitive tapping the mantle area since these patients especially children can develop severe stiffness or respiratory compromise.

**Palatal myoclonus** has unique clinical features and distribution. It is not difficult to recognize by pattern recognition, if oral examination is not overlooked, especially in patients presenting with ear clicks or oscillopsia from co-existing pendular nystagmus.

Differential diagnoses of subcortical and brainstem myoclonus

Differential diagnosis of subcortical myoclonus was mentioned above. Hyperekplexia and palatal myoclonus are forms of brainstem myoclonus. In addition, it is also important to recognize brainstem origin of myoclonus especially when temporal profile is acute-to-subacute, since further detail investigations searching for **brainstem structural lesions, postinfectious and paraneoplastic processes** (e.g**. opsoclonus-myoclonus ataxia syndrome and progressive encephalomyelitis with rigidity and myoclonus or PERM** due to anti-glycine receptor antibody in some cases) involving the brainstem are crucial. **Reticular reflex myoclonus** typically involves lower brainstem and upper cervical region leading to axial jerks, especially neck flexion. It is generally seen in some patients with posthypoxic myoclonus and provides supportive evidence of brainstem contributions, in addition to cortical origin. Reticular reflex myoclonus by itself is a phenomenologic feature, rather than a diagnosis. Clinical pearls of some selected disorders presenting with subcortical and brainstem myoclonus are summarized in Table 1.

## III. Spinal myoclonus

General phenomenologic features

Two forms of spinal myoclonus include **spinal segmental myoclonus** and **propriospinal myoclonus**. Generally jerks in spinal myoclonus tend to be slower compared to cortical and brainstem myoclonus, correlating with their relatively longer duration of EMG bursts. Distribution of myoclonus is very different between these two forms. Spinal segmental myoclonus involves muscles in one or multiple myotomes corresponding to spinal segment(s). It is important not to miss a structural lesion by obtaining appropriate spinal neuroimaging.

Patients with propriospinal myoclonus have axial jerks, typically truncal flexion. This corresponds to electrophysiologic studies which reveal myoclonic jerks start in a spinal segment, then spread to rostral and caudal segments. Patients usually have reflex myoclonus after tactile stimulation, but the latency between the stimulus and myoclonic jerks is long due to slow-conducting propriospinal pathways, as opposed to fast-conducting pathway in cortical myoclonus. Propriospinal pathway helps in coordination between forelimbs and hindlimbs during walking in quadrupeds. However, its existence in humans remains unclear. There have

been studies demonstrating a psychogenic nature of propriospinal myoclonus, given the presence of Bereitschaftspotential, a signature of voluntary movement, prior to the jerks. However, some studies demonstrated white matter tract disruption on diffusion tensor imaging studies in propriospinal myoclonus, indicating microstructural lesions. In our opinion, both organic and psychogenic forms may exist, and it may be premature to conclude that all patients with propriospinal myoclonus are psychogenic. Of note, differential diagnoses of axial jerks/myoclonus include propriospinal myoclonus and reticular reflex myoclonus (discussed under "brainstem myoclonus").

Differential diagnoses of spinal myoclonus

These include spinal segmental myoclonus and propriospinal myoclonus, as mentioned above. Clinical pearls of some selected disorders presenting with spinal myoclonus are summarized in Table 1. It is important to always look for structural lesions in the spinal cord in these forms of myoclonus.

## IV. Peripheral myoclonus

Peripheral myoclonus can be associated with focal lesions in the nerve roots, plexuses or peripheral nerves. Distribution of myoclonic jerks corresponds to their anatomical locations: along dermatomal, plexus or peripheral nerve distribution. Similar to spinal myoclonus, it is important to search for structural lesions with appropriate neuroimaging studies such as MRI with focus to the region(s) of interest, or nerve ultrasonography. Another unique and common form of peripheral myoclonus is hemifacial spasm. The detail has been provided in Table 1.

## Treatment of myoclonus

Treatment of myoclonus can be divided into specific and symptomatic therapies. As a general principle, specific therapies should be employed when possible. Thus, it is important not to miss some treatable diagnoses as we discussed above such as opsoclonus-myoclonus ataxia syndrome or PERM where immunotherapies have an important role.

For symptomatic therapies, three conventional medications include levetiracetam, clonazepam and valproic acid. Anatomical localization of myoclonus can roughly guide selection of pharmacological therapies. As a general principle, levetiracetam is considered as first-line in cortical myoclonus, whereas clonazepam is first-line in brainstem and spinal myoclonus. If myoclonus is not controlled with one medication, then the other two can be switched to, or more commonly, added. Table 2 demonstrates the doses of conventional medications for symptomatic therapy of myoclonus.

Other less commonly used medications include zonisamide and sodium oxybate (in posthypoxic myoclonus which is alcohol-responsive). Sodium oxybate is a GABA derivative that has mechanism of action similar to alcohol, but less sedation side effect. It has been FDA-approved in the U.S. to treat excessive daytime sleepiness and cataplexy in narcolepsy. However, its use in alcohol-responsive movement disorders (Table 3) remains off-label.

Botulinum toxin injections are the treatment of choice in hemifacial spasm. Microvascular decompression has rarely performed in our clinical practice. Although there have been studies demonstrating benefits, the recurrence rate is high.

Deep brain stimulation (DBS) is not generally performed in myoclonus except in myoclonus-dystonia syndrome. Globus pallidus interna (GPi) target improves both myoclonus and dystonia (hence preferable target), whereas ventral intermediate nucleus (Vim) improves only myoclonus.

**Table 2.** Suggested doses of conventional pharmacological treatment of myoclonus

| Conventional pharmacological treatment of myoclonus | |
|---|---|
| **Medication** | **Dose (mg/day)** |
| Levetiracetam | 500-2,000 |
| Clonazepam | 0.5-2 |
| Valproic acid | 750-1,500 |

**Table 3.** List of movement disorders that are alcohol-responsive

| Alcohol-responsive movement disorders |
|---|
| ➢ Posthypoxic myoclonus |
| ➢ Myoclonus-dystonia syndrome |
| ➢ Spasmodic dysphonia |
| ➢ Essential tremor |

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**Selected references**

Armangue T, Sabater L, Torres-Vega E, et al. Clinical and Immunological Features of Opsoclonus-Myoclonus Syndrome in the Era of Neuronal Cell Surface Antibodies. *JAMA Neurol*. 2016;73:417-424.

Carvajal-Gonzalez A, Leite MI, Waters P, et al. Glycine receptor antibodies in PERM and related syndromes: characteristics, clinical features and outcomes. *Brain*. 2014;137:2178-2192.

Caviness JN, Brown P. Myoclonus: current concepts and recent advances. *Lancet Neurol*. 2004;3:598-607.

Fahn S, Marsden CD, Van Woert MH. Definition and classification of myoclonus. *Adv Neurol*. 1986;43:1-5.

Frucht SJ, Houghton WC, Bordelon Y, et al. A single-blind, open-label trial of sodium oxybate for myoclonus and essential tremor. *Neurology*. 2005;65:1967-1969.

Gupta HV, Caviness JN. Post-hypoxic Myoclonus: Current Concepts, Neurophysiology, and Treatment. *Tremor Other Hyperkinet Mov (N Y)*. 2016;6:409.

Ikeda A, Kakigi R, Funai N, et al. Cortical tremor: a variant of cortical reflex myoclonus. *Neurology*. 1990;40:1561-1565.

Kalviainen R. Progressive Myoclonus Epilepsies. *Semin Neurol*. 2015;35:293-299.

McKeon A, Vincent A. Autoimmune movement disorders. *Handb Clin Neurol*. 2016;133:301-315.

Roze E, Bounolleau P, Ducreux D, et al. Propriospinal myoclonus revisited: Clinical, neurophysiologic, and neuroradiologic findings. *Neurology*. 2009;72:1301-1309.

Rughani AI, Lozano AM. Surgical treatment of myoclonus dystonia syndrome. *Mov Disord*. 2013;28:282-287.

Samuel M, Torun N, Tuite PJ, et al. Progressive ataxia and palatal tremor (PAPT): clinical and MRI assessment with review of palatal tremors. *Brain*. 2004;127:1252-1268.

Shibasaki H, Hallett M. Electrophysiological studies of myoclonus. *Muscle Nerve*. 2005;31:157-174.

Termsarasab P, Thammongkolchai T, Frucht SJ. Spinal-generated movement disorders: a clinical review. *J Clin Mov Disord*. 2015;2:18.

Thomas RH, Chung SK, Wood SE, et al. Genotype-phenotype correlations in hyperekplexia: apnoeas, learning difficulties and speech delay. *Brain*. 2013;136:3085-3095.

van Rootselaar AF, van Schaik IN, van den Maagdenberg AM, et al. Familial cortical myoclonic tremor with epilepsy: a single syndromic classification for a group of pedigrees bearing common features. *Mov Disord*. 2005;20:665-673.

Zutt R, van Egmond ME, Elting JW, et al. A novel diagnostic approach to patients with myoclonus. *Nat Rev Neurol*. 2015;11:687-697.