Myoclonus

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ABSTRACT: Myoclonus refers to brief muscle jerks caused by neuronal discharges. Etiologies are numerous, ranging from physiological jerks to myoclonus secondary to severe neurodegenerative conditions. The source of myoclonus may be in the cerebral cortex, the brain stem or the spinal cord and multiple generators may be involved in a single patient. The clinical approach to myoclonus relies on both etiological and physiological classifications. Pharmacological therapy is largely based on the presumed site of origin of myoclonus. Polytherapy may be required, particularly in severe cases of cortical myoclonus.

RéSUMÉ: La myoclonie. La myoclonie désigne des secousses musculaires brèves causées par des décharges neuronales. L’étiologie est variée, allant de secousses physiologiques à des myoclonies secondaires à des maladies neurodégénératives sévères. La source des myoclonies peut provenir du cortex cérébral, du tronc cérébral ou de la moelle épinière et des sources multiples peuvent coexister chez le même patient. L’approche clinique est basée sur des classifications étiologiques et physiologiques. Le traitement pharmacologique est basé en grande partie sur le site d’origine présumé des myoclonies. Une polythérapie peut être nécessaire, particulièrement chez les cas sévères de myoclonies d’origine corticale.


SYMPTOMATOLOGY

Myoclonus refers to sudden, brief muscle jerks, irregular or rhythmic, not associated with a loss of consciousness, arising within the central nervous system. We therefore exclude muscle twitching, (i.e. fasciculation) which may be seen in various peripheral disorders. Myoclonic jerks usually represent brief muscle contractions ("positive myoclonus") but may also be produced by equally brief lapses of muscle contraction ("negative myoclonus"), and both types may be observed in the same patient, such as in posthypoxic action myoclonus.

Most often, myoclonus is easily distinguished from other dyskinesias. Tics may present as brief muscle jerks but are usually complex, stereotyped movements accompanied by an urge to move, with relief of this inner tension once the tic has occurred. Unlike myoclonic jerks, tics can be controlled by an effort of will, at least temporarily. Describing tics as “clonic” or “dystonic” refers only to their duration and clinical pattern and must not be understood as implying a different underlying mechanism. Tics have little impact on voluntary movements, unlike myoclonus.

Rhythmic myoclonus may be confused with tremor. Its frequency is often slower than the commonly observed tremors, it is present at rest, is not modified significantly by voluntary movements and often persists during sleep. Its “square-wave” character, with an interval between each brief burst, differs from the more sinusoidal character of tremor, seen in essential tremor.1 An uncommon form of tremor, described by Ikeda et al2 showed synchronous activation of agonist and antagonists at frequencies of 9 to 18 Hz with an associated cortical potential on electroencephalogram (EEG) back averaging.

Myoclonus may also be confused with chorea, especially if multifocal and asynchronous. The constant flow of randomly distributed muscle jerks, occurring unexpectedly, is characteristic of chorea, contrasting with the often distinctive and repetitive pattern of muscle jerking of myoclonus. Finally, dystonia is easily distinguished from myoclonus by the more sustained, twisting character of the spasms with resulting characteristic dystonic postures.

CLASSIFICATION

There are several methods of classifying myoclonus (Table). Clinically, myoclonus can be described as focal, multifocal, axial or generalised, involving both arms and legs simultaneously. The muscle jerks may occur spontaneously, in response to various stimuli, particularly muscle stretch but also light touch, noise, light (reflex or stimulus sensitive myoclonus) or on volition (action myoclonus). Many patients will show a variable combination of the above. Although this classification is purely

Suppl. 1 – S53

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https://doi.org/10.1017/S0317167100003243 Published online by Cambridge University Press
The dystonia tends to involve the neck and shoulder. Initially described in a case of focal dystonia, it is usually symptomatic of a focal, potentially treatable, structural lesion. It is rather the history (mode of onset, progression, hereditary transmission, etc.) and the associated clinical signs that will guide the clinician to the appropriate diagnosis and relevant investigation.

Myoclonus can also be classified on the basis of its cause. Since numerous, unrelated neurological conditions may lead to myoclonus, it is preferable to regroup them into a few broad categories, namely:

1. Physiological myoclonus
2. Essential myoclonus
3. Epileptic myoclonus
4. Symptomatic myoclonus

### 1. Physiological myoclonus

Myoclonic jerks may occur in normal individuals. Common examples include hiccups (a form of diaphragmatic myoclonus) and hypnic jerks.

### 2. Essential myoclonus

This is a benign, uncommon condition seen in otherwise neurologically normal individuals. Both sporadic and familial (autosomal dominant) cases have been described.

The main features are:
- Onset in the first and second decade of life
- Males and females equally affected
- Benign course compatible with an active life of normal span
- Absence of seizures, ataxia or other neurological deficits
- Normal EEG and somatosensory evoked potentials (SEPs)

The jerks involve preferentially the face, trunk and the proximal muscles of the limbs. They are usually multifocal (sometimes generalised), of lesser severity at rest and increase on volition. Although widespread in distribution, the jerks seem to cause little disability, owing to their relatively small amplitude. Other distinctive features described in some families include a dramatic response to alcohol and a close association with a postural tremor similar to that observed in patients with essential tremor. In some families, dystonic postures and movements are present to a variable degree in combination with myoclonic jerks. The dystonia tends to involve the neck and shoulder muscles, whereas myoclonic jerks affect more distal muscles of the upper limbs. Legs are less involved. Both myoclonus and dystonia may respond dramatically to alcohol.

Some authors have also included the periodic movements of sleep (“nocturnal myoclonus”) in the category of essential myoclonus. These jerks tend to occur in a repetitive fashion, every 30 seconds or so, but are much too long in duration (1.5 - 2.5 s) to be called “myoclonic”. The appellation of “periodic movements of sleep” seems more appropriate.

### 3. Epileptic myoclonus

Here are included the numerous conditions where myoclonus is a component of a disorder dominated by one or, more commonly, many types of seizures. One of the manifestations of the epileptic attacks is myoclonic jerks. The association with other types of seizures, particularly tonic-clonic seizures and the presence of epileptiform abnormalities on surface EEG are useful in establishing the epileptic nature of the myoclonus.

Epileptic myoclonus may be generalised or focal. The former is essentially a problem of children and of adolescents, such as in the primary generalised epilepsies or with other, less favourable, conditions such as the West syndrome or the Lennox-Gastaut syndrome. These conditions are well-known and will not be discussed further.

Epilepsia partialis continuitis deserves further comment, since it is usually symptomatic of a focal, potentially treatable, structural lesion. Initially described in a case of focal encephalitis, it can also be seen with abscess, tumour, arteriovenous malformation (AVM), granuloma, contusion, infarction or demyelination; both cortical and subcortical areas may be involved alone or in combination. The jerking may be rhythmic or arhythmic, varying from one every few seconds to many times per second. The frequency, distribution and amplitude of the jerking vary from moment to moment and from day to day. The hand, particularly the finger flexors, is most often involved. The jerks may spread to cause a typical Jacksonian motor seizure, and a generalised tonic-clonic fit (Figure). Epilepsia partialis continuitis may persist for years and is usually poorly responsive to anticonvulsants. In some cases, surgical resection of the epileptic focus may provide relief.

### 4. Symptomatic myoclonus

This vast category is made up of various widespread encephalopathies, either progressive (e.g. lipid storage diseases) or static, where myoclonus is one of the clinical manifestations. The features of myoclonus are not distinctive. It is rather the presence of epileptiform abnormalities on surface EEG are useful in establishing the epileptic nature of the myoclonus.

All the potentially treatable conditions such as the metabolic encephalopathies (uraemic, hepatic), those induced by various drugs, usually at toxic levels (L-dopa, tricyclic, lithium, anticonvulsants) and the less common toxic (bromides, bismuth) encephalopathies, must be excluded. Besides the decreased level of sensorium, one can expect to find asterixis (negative myoclonus), along with multifocal, asynchronous, arhythmic myoclonus occurring spontaneously and/or in response to various stimuli and volition.

Static myoclonic encephalopathies do not usually pose a diagnostic problem. Cerebral anoxia, such as following a cardiac arrest or an episode of respiratory failure, may be the cause of an incapacitating myoclonic syndrome. There is an initial period of coma during which myoclonus and generalised seizures may occur. On the recovery, multifocal and generalised jerks,
predominantly activated by walking or motor tasks requiring precision, dominate the clinical picture. Myoclonus is usually stimulus sensitive and may also occur spontaneously. The myoclonus induced by walking often appears to be the most resistant to treatment; that, in addition to coexistent negative myoclonus, cerebellar ataxia and, not least, a permanent fear of falling, may confine the patient to a wheelchair.

Diagnostic difficulties are more likely to arise when dealing with patients presenting degenerative conditions, such as neuronal storage diseases where myoclonus (often multifocal, asymmetrical, mostly in response to stimuli and/or volition) is part of the clinical picture. These conditions are fortunately rare, despite the vast amount of literature on the subject. Most are familial, with an autosomal recessive mode of inheritance, begin during childhood, and are characterised by myoclonic as well or other types of seizures, particularly tonic-clonic. Although myoclonus and seizures may initially dominate the clinical picture and suggest an alternate diagnosis, such as the juvenile myoclonic epilepsy of Janz, the development of progressive neurologic dysfunction usually dominated by ataxia and cognitive deterioration characterises this heterogeneous group of patients.

The main causes of progressive myoclonic syndromes are Unverricht-Lundborg disease (“Baltic” myoclonus), Lafora-body disease, the neuronal ceroid-lipofuscinosis, the sialidosis and the increasingly recognised mitochondrial disease. Each of these disorders may be associated with spontaneous, multifocal and generalised myoclonic jerks that may be stimulus sensitive and exacerbated by volition. Given the clinical similarities between these various conditions, exhaustive investigation will be necessary to establish a definite diagnosis. This will include urinary dolichol estimation (lipofuscinosis), urinary thin layer chromatography for oligosaccharides (sialidosis), urinary organic acid chromatography (biotin responsive encephalopathy), along with hexosaminidase A and B screen of serum and leucocytes for GM\textsubscript{2} gangliosidosis. Tissue examination is also essential; skin and muscle biopsy will assist the diagnosis of Lafora-body disease, lipofuscinosis and mitochondrial disease. Specific enzyme essays can be performed, if clinically relevant, for some conditions such as Gaucher’s disease (β glucocerebrosidase) or the sialidosis (-N-acetyl-neuraminidase, β-galactosidase).

Myoclonus can also be a feature of some adult-onset degenerative conditions, often in association with progressive cognitive dysfunction. In Alzheimer’s disease, myoclonus is more likely to occur at a late stage when dementia is severe, and tends to affect distal muscles, both spontaneously and in response to various stimuli. In Creutzfeldt-Jakob disease, myoclonus is much more frequent and tends to be generalised, although focal jerking (face, limb) may be seen initially. Again the jerks occur mostly spontaneously, but also in response to various stimuli and on volition. The rapidly progressive dementia, the associated neurological features such as cortical blindness, pyramidal, cerebellar or extrapyramidal (most often parkinsonism) signs, and the typical periodic EEG discharges help distinguish this rare entity from the more common Alzheimer’s disease.

Myoclonus is now recognised as an important clinical feature of many basal ganglia disorders. In corticobasal degeneration, many patients will present focal, usually upper limb myoclonus most prominent on voluntary action or in response to sensory stimulation. A cortical origin is suspected given the known cortical pathology, the combination of focal, predominantly distal hypersynchronous jerks, and the enhanced cortical...
Patients with Huntington's disease may exhibit this extensive spread of myoclonus reflecting arrival of the sensory volley in the cortex, usually of normal size. Since the giant SEP is not seen in other types of myoclonus, its demonstration is diagnostically significant. Drugs like clonazepam or lisuride possibly act on the interconnection between these two areas of cortex, since they significantly reduce myoclonic jerking without reducing the amplitude of the SEP.

In many patients, the cortical reflex or action myoclonus remains focal, involving the stimulated or active limb, suggesting an exaggeration of cortical long loop reflexes and intracortical processing of motor activity. In some, however, more extensive myoclonic jerks (ipsilateral limb, bilateral or generalised) suggest additional disinhibition, with intrahemispheric and interhemispheric spread of excitation via cortico-cortical and transcallosal pathways. This extensive spread of excitation must be relevant to the generalisation of seizures usually seen in these patients. In others, the jerks may become repetitive, spread into a Jacksonian motor fit and a generalised seizure (Figure). Cortical myoclonus can therefore be considered as a fragment of focal epilepsy.

Therapeutic interventions will concentrate on increasing cortical inhibitory activity and try to prevent the spreading of neuronal excitation.

Cortical myoclonus is commonly seen in patients with progressive myoclonic epilepsy, posthypoxic action myoclonus, metabolic toxic encephalopathies, focal cortical lesions (stroke, AVM, tumour, etc.) and in various degenerative diseases involving the cortex such as Alzheimer’s disease and corticobasal degeneration.

2. Reticular myoclonus

Like cortical myoclonus, reticular myoclonus may occur spontaneously, in response to a wide variety of peripheral stimuli or during voluntary action. The jerks are equally brief, lasting between 10-30 ms. There are, however, some distinctive features.

• The jerks tend to be generalised (for example, a tap to a single part of the body may induce a generalised muscle jerk in patients with a stimulus sensitive form). Axial and proximal muscles are mainly involved, causing neck flexion, shoulder elevation along with trunk and knee extension.
• The cortical EEG correlate, if present, is not time-locked to the EMG event, and the SEPs not enlarged.
• The sequence of activation of muscles is different, i.e. up the brainstem and down the spinal cord. Specifically, the trapezius (XIth cranial nerve) is activated first, suggesting an origin at the level of the medulla.

Reticular myoclonus, both spontaneous and reflex, may be seen in metabolic encephalopathies, postanoxic myoclonus and conventional surface EEG and may need back averaging).

• Enlarged somatosensory evoked potentials (especially with reflex myoclonus).1

Cortical myoclonus is often stimulus sensitive, with muscle stretch often being the critical stimulus. This selectivity of stimulus is more easily explained if the sensory rather than the motor cortex is hyperexcitable. Most patients with cortical reflex myoclonus indeed show enlarged SEP following electrical stimulation of peripheral nerves; with median nerve stimulation, the P25-N33 component is enlarged, whereas the first major corticocortical negative peak (N20) reflecting arrival of the sensory volley in the cortex, is usually of normal size. Since the giant SEPs not seen in other types of myoclonus, its demonstration is diagnostically significant. Drugs like clonazepam or lisuride possibly act on the interconnection between these two areas of cortex, since they significantly reduce myoclonic jerking without reducing the amplitude of the SEP.

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1. Cortical myoclonus

The most common form of myoclonus observed clinically results from abnormal electrical discharges arising in the cerebral cortex.

The main features of cortical myoclonus are:

• Brief EMG burst (10-30ms).
• Jerk often confined to one part of the body.
• Activation of muscles in a rostro-caudal sequence.
• Time locked cortical event preceding spontaneous or action-induced jerking (this event may not be detectable by

Various inflammatory conditions, such as acute viral encephalitis or postinfectious encephalomyelitis, may be associated with myoclonus, usually multifocal, or generalised. Paraneoplastic encephalitis may give rise to a distinct clinical syndrome, opsoclonus-myoclonus, often associated with ataxia and encephalopathy. More commonly seen in infants (6-18 months) with a underlying neuroblastoma, it may also occur in adults, usually with a lung carcinoma. A similar clinical picture may be observed in other inflammatory conditions involving the brainstem, such as the rare but treatable Whipple’s disease. The latter has also been associated with a distinct form of segmental myoclonus “oculomasticatory myorhythmia”.16

It will be emphasised that for most patients with symptomatic myoclonus, a definitive diagnosis can be reached with careful clinical history and examination, along with simple procedures such as surface EEG and MRI. Only a minority will need an extensive battery of tests, including skin, muscle biopsies or exotic enzyme assays.

PHYSIOLOGY OF MYOCLOONUS

Another approach to myoclonus is based on physiology, focusing on the mechanisms and the location of presumed abnormal neuronal activity. Such studies have not only provided us with a better understanding of the phenomenon, but may also assist defining better strategies of therapy. Myoclonus can be

1. cortical,
2. subcortical (reticular) or
3. segmental, the latter originating from the brain stem or the spinal cord.

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https://doi.org/10.1017/S0317167100003243 Published online by Cambridge University Press
in progressive myoclonic epilepsies. Both cortical and reticular myoclonus may be present in the same patient, reflecting hyperexcitability at multiple levels of the central nervous system. The exaggerated startle response, whether idiopathic, hereditary or symptomatic (static encephalopathies, brainstem encephalitis or structural lesions) is also considered as a form of brainstem reticular myoclonus. Unlike reticular reflex myoclonus, spontaneous jerks are uncommon, and are mostly evoked by sudden noise or light, instead of muscle stretch or volition.4

3. Segmental myoclonus

Segmental myoclonus is usually indicative of a focal structural lesion and its clinical features are rather distinctive. The jerks are usually rhythmic, tend to persist during sleep and are usually not stimulus sensitive. There is no EEG correlate and the SEPs are not enlarged. The best known condition is palatal myoclonus, which:
• May be uni- or bilateral
• May be associated with contraction of external ocular muscles, those of larynx, neck, diaphragm, trunk and limbs.
• Has a rhythm of about 2Hz (range 80-180/min) and is most often due to brainstem stroke, although it has been reported with multiple sclerosis, brainstem tumours, syringomalacia, obstructive hydrocephalus and encephalitis.21
• The median interval between the precipitating cause and the onset of palatal myoclonus is about 10 months. The precise pathological mechanism underlying this condition has yet to be defined, but the most likely explanation of symptomatic palatal myoclonus is that a lesion involving the dentato-olivary tract causes the cells of the inferior olive to oscillate independently. The increased glucose-uptake in the area of the inferior olive on PET scanning supports that hypothesis.22
In a minority of cases, no causes is evident (“essential palatal myoclonus”). The age of onset is then considerably younger (25 y vs 45 y for symptomatic palatal myoclonus), and the presenting complaint usually consists of an ear click.23
• The muscle involved is the tensor veli palatini, bringing the soft palate upward. Unlike the symptomformic condition, there is no evidence for hypertrophic degeneration of the inferior olive, and the MRI is normal.24

Segmental myoclonus of spinal origin involves muscles controlled by one or a few contiguous segments of the spinal cord.24,25 Again the jerking tends to be rhythmic and unaffected by peripheral stimuli, although it may worsen with change in limb position or mental stress. Sleep may or may not abolish the myoclonus. The underlying pathology may be a tumour, infection (herpes zoster), AVM, demyelination or a compressive myelopathy. Spinal myoclonus can also follow spinal anaesthesia, usually lasting a few hours or days.26

Propriospinal myoclonus is a less common form of myoclonus, involving activity over extensive lengths of the spinal cord rather than a segmental distribution.27 The jerks tend to be repetitive and cause symmetrical, often violent, axial flexion. The neck, trunk, hip and knees may be involved. They occur spontaneously, often occur during sleep, and may be elicited by taps to the trunk and limbs. Surface recordings suggest that the myoclonic discharges spread up and down from a spinal generator. The involvement of propriospinal pathways is suggested by the pattern of muscles recruitment (trunk and proximal limbs bilaterally) and the relatively slow conduction velocity, with latencies between stimuli and reflex response in the order of 100 ms.28

TREATMENT

Before we discuss the therapeutic strategies currently used for the various types of myoclonus, we shall briefly review some biochemical aspects of myoclonus along with the possible mechanisms of action of the main antmyoclonic agents.

Many neurotransmitter systems play an important, albeit imperfectly understood, role in human myoclonus. There is good evidence, both in animal models and in humans, that brain serotonin (5-HT [hydroxytryptamine]) deficiency may produce certain types of myoclonus:
• In posthypoxic action myoclonus, CSF 5-HIAA (the principal metabolite of 5-HT) levels are reduced. The myoclonus may respond dramatically to 5-HT precursor 5-HTP, especially if administered with carbidopa (to prevent peripheral decarboxylation) or 5-HT reuptake blockers. Similar findings may be observed in patients with post-traumatic myoclonus or progressive myoclonic epilepsy. Methysergide, a 5-HT antagonist, blocks the therapeutic action of 5-HTP + carbidopa.29
• Animal model of reticular reflex myoclonus, by injection of pp – DDT (1,1,1, trichloro – 2,2 bis p chlorophenyl ethane) into medullar reticular formation, is improved with 5-HT agonist and aggravated by 5-HT antagonists.30
• In the Papio papio photosensitive baboon, the bilateral myoclonic jerking induced by a photic stimulation can be greatly reduced or even suppressed by 5-HT agonists.30

Patients with posthypoxic action myoclonus are those that show greatest improvement with 5-HTP + carbidopa, although patients with other etiologies of action myoclonus may also improve.29 This therapy is not without side effects (nausea, vomiting, diarrhea, agitation, etc.), and has been replaced by drugs such as sodium valproate and clonazepam.

A disorder of gamma amino butyric acid (GABA) inhibitory activity is often postulated to be the mechanism responsible for the origin of focal epilepsy and, by extension, cortical myoclonus. Indeed, injection into the rat motor cortex of a GABA antagonist (picrotoxin, bicuculline) induces focal myoclonic jerking, blocked by local injection of GABA.31

In patients with posthypoxic myoclonus and progressive myoclonus epilepsy, a reduction of 25-50% of GABA levels in the CSF has been found.30 Drugs that enhance GABA levels in the CNS may therefore exert antmyoclonic activity.

Anticholinergic drugs have been occasionally beneficial in patients with essential myoclonus or palatal myoclonus, but overall the cholinergic system does not seem to play a significant role in most forms of myoclonus. A similar comment applies to the dopaminergic system except in photically induced cortical myoclonus, where apomorphine or levodopa can have a dramatic effect.33

The drugs more commonly used in myoclonus are sodium valproate, clonazepam, and primidone. Piracetam and lisuride also demonstrate antmyoclonic activity but are not commercially available in this country.

Sodium valproate has numerous biochemical effects, but the
mechanism of its antomyoclonic action remains poorly understood.\textsuperscript{14}

Clonazepam is a powerful antomyoclonic agent. Its main action is its ability to interact with benzodiazepine receptors that facilitate GABAergic transmission.\textsuperscript{15}

Primidone is believed to enhance postsynaptic GABA-mediated inhibition by acting on the GABA receptor complex which contains a modulatory receptor site for barbiturates.\textsuperscript{18}

Cortical myoclonus, whether spontaneous, stimulus sensitive or action induced, responds best to sodium valproate and clonazepam. Although polytherapy is often required for best results, especially in severe disabling action myoclonus, it is reasonable to start with sodium valproate, and to add clonazepam later, if necessary.\textsuperscript{18} Some tolerance to clonazepam may occur so clobazam may become an alternative. If disability remains, a third drug, primidone, may be added. Piracetam, widely used in Europe, is also very effective for cortical myoclonus. Negative myoclonus (asterixis) often coexists in patients with cortical action myoclonus and may contribute to their disability. There is no information in the literature about the effect of antomyoclonic drugs on this form of myoclonus.\textsuperscript{18}

The best drug for brainstem myoclonus is clonazepam, although sodium valproate may also be effective.\textsuperscript{20} It must be emphasized that both types of myoclonus, cortical and reticular, may coexist in the same patient, and may thus be more effectively controlled by polytherapy.

Palatal myoclonus is often resistant to drug therapy but has occasionally responded to anticholinergics and clonazepam. Injection of botulinum toxin into the tensor veli palatini for patients with essential palatal myoclonus may prove valuable in reducing the annoying ear click.

Spinal (segmental) myoclonus is best controlled by clonazepam, although many drugs have been reported to show some efficacy, including sodium valproate, carbamazepine, tetrazenazine and trihexyphenidyl.\textsuperscript{25} There has been no study on the medical treatment of propriospinal myoclonus; one of the cases described improved after surgical corrections of the offending lesion.\textsuperscript{28}

\textbf{REFERENCES}


