Myoclonus- A Review

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Abstract

Myoclonus is a hyperkinetic movement disorder characterized by a sudden, brief, involuntary jerk. Positive myoclonus is caused by abrupt muscle contractions, while negative myoclonus by sudden cessation of ongoing muscular contractions. Myoclonus can be classified in various ways according to body distribution, relation to activity, neurophysiology, and etiology. The neurophysiological classification of myoclonus by means of electrophysiological tests is helpful in guiding the best therapeutic strategy. Given the diverse etiologies of myoclonus, a thorough history and detailed physical examination are key to the evaluation of myoclonus. These along with basic laboratory testing and neurophysiological studies help in narrowing down the clinical possibilities. Though symptomatic treatment is required in the majority of cases, treatment of the underlying etiology should be the primary aim whenever possible. Symptomatic treatment is often not satisfactory, and a combination of different drugs is often required to control the myoclonus. This review addresses the etiology, classification, clinical approach, and management of myoclonus.

Keywords: Classification, electrophysiology, etiology, myoclonus, treatment

INTRODUCTION

Myoclonus is defined as a sudden, brief, shock-like, involuntary movement caused by muscular contractions or inhibition.[1] Patients usually describe myoclonus as "jerks" or "shakes." Muscle contractions produce positive myoclonus, while inhibition of ongoing muscle contractions produces negative myoclonus (NM). In 1881, Friedreich proposed the term "myoclonus" in his original report, which described a 50-year-old man presenting with involuntary small muscle jerks at rest, and called it "paramyoclonus multiplex."[2] Very little is known about the epidemiology of myoclonus as it has a wide spectrum of associated clinical manifestations and numerous causes.[3] The only available epidemiological study of myoclonus consisting of a defined population recruited in Olmsted County from 1976 to 1990, revealed a lifetime prevalence of myoclonus of 8.6 cases per 1,00,000 people.[4]

Myoclonus is both sudden and brief ("jerk-like") when compared to other involuntary movements. It has to be clinically differentiated from other movement disorders, which are jerky such as tics, chorea, and jerky dystonia often called "dystonic myoclonus." Myoclonus is distinguished from tics by the absence of an urge to perform a movement, lack of suppressibility, or relief of tension following the movement which is typical in tics. Chorea is characterized by dance-like but nonstereotyped movements that flow from one body part to another. Dystonic movements are slower and consist of continuous or intermittent abnormal twisting movements and/or sustained postures. Occasionally, dystonic movements can be jerky, but the presence of twisting movements or posturing during muscle contractions distinguishes it from myoclonus. Besides, dystonic jerks do not have the lightning-like speed of myoclonus. The rhythmic repetitive nature of cortical myoclonus in the fingers can resemble tremors.

METHODS

The relevant studies on myoclonus were reviewed using PubMed search till 31st October 2020. A total of 10,705 articles for myoclonus or cortical or subcortical myoclonus, 505 articles on the classification of myoclonus, 6602 articles on etiology of myoclonus, 3469 articles on the pathophysiology of myoclonus, 1631 articles on cortical myoclonus, 1052 articles on brainstem myoclonus, 422 articles on hyperekplexia, 1047 articles on startle syndromes, 98 articles on propriospinal myoclonus, 714 articles on spinal segmental myoclonus, 314 articles on essential myoclonus, 381 articles on peripheral myoclonus, 114 articles on psychogenic myoclonus, 121 articles on the electrophysiology of myoclonus, and 4558 articles on the treatment of myoclonus were found. The cross-references of the relevant articles were also reviewed.

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CLINICAL PRESENTATION AND CLASSIFICATION

The first attempt to classify myoclonus was in 1903 by Lundborg. He classified it into three groups: essential myoclonus, symptomatic myoclonus, and familial myoclonic epilepsy. With a better understanding of its etiology and pathophysiology over subsequent decades, new schemes of classification evolved. Myoclonus is currently classified according to anatomical distribution, relation to activity, and precipitating factors detected on examination, neurophysiology, and etiology [Figure 1].

Based on body distribution, myoclonus is classified as focal, multifocal, segmental, or generalized. Based on relation to activity, it can be differentiated as myoclonus occurring at rest, during an action, or maintaining a posture.[5] Myoclonus can be provoked by tactile, acoustic, or visual stimuli (reflex or stimulus sensitive myoclonus). Cortical myoclonus usually tends to be either focal or multifocal, and it is particularly aggravated by action and tactile stimuli. Cortical-subcortical myoclonus, typically seen in generalized epilepsy syndromes, is usually generalized or multifocal and occurs at rest. However, it can be stimulus sensitive. Brainstem reticular reflex myoclonus is of subcortical-nonsegmental origin and is mostly generalized, synchronously involving both the arms proximally as well as the neck, face, trunk, and lower limbs. These jerks are more flexor than extensor, occur at rest and during action and are induced by auditory or tactile stimuli such as tapping on the limbs or face.[6] Segmental, unilateral arrhythmic jerking in the arm and/or trunk is typical of spinal segmental myoclonus, whereas jerking of the trunk and abdomen along with limbs bilaterally may be due to "propriospinal myoclonus" which is another type of subcortical, nonsegmental myoclonus. Peripheral myoclonus is typically focal, and the classical example is hemifacial spasm, usually resulting from irritation of the facial nerve in the cerebellopontine angle region due to neuro-vascular conflict.

NEUROPHYSIOLOGICAL CLASSIFICATION

The neurophysiological classification of myoclonus focuses on the pathophysiologic generator of myoclonus, and the mechanisms of propagation, regardless of its clinical presentation.[7,8] A single disease can have myoclonus caused by different mechanisms. For example, in posthypoxic myoclonus (Lance-Adams syndrome), both cortical myoclonus and brainstem reticular reflex myoclonus may coexist.[7] Also, myoclonus due to the same neurophysiological mechanism (e.g., segmental) can vary in its anatomical location (e.g., brainstem or spinal cord). Hence, physiological classification is complementary to the clinical presentation.[9] Identifying the physiological category also guides in deciding the most effective treatment,[5] as drugs that are effective in cortical myoclonus may not be effective in other types of myoclonus. The tests used to classify myoclonus neurophysiologically are electroencephalography (EEG), surface electromyography (EMG), EEG–EMG polygraphy with back-averaging, somatosensory evoked potentials (SEP), long latency C-reflex, cortical-muscular coherence, transcranial magnetic stimulation, jerk-locked evoked potentials, and magnetoencephalography (MEG).[2] The physiological categories of myoclonus include the following:

a. Cortical
b. Cortical-subcortical
c. Subcortical-nonsegmental (includes brainstem reticular reflex myoclonus, hyperekplexia, and propriospinal myoclonus)
d. Segmental (includes palatal myoclonus and spinal segmental myoclonus)
e. Peripheral

Cortical myoclonus

It is the most common form of myoclonus in clinical practice. The neurophysiological hallmark of cortical myoclonus is abnormal hyperexcitability of the sensorimotor cortex.[10] The pyramidal neurons of the layer III and V become hyperexcitable, likely related to gamma-aminobutyric acid (GABA)-ergic mechanisms and abnormal cortico-thalamic connectivity.[11] Numerous other abnormalities including aberrations in serotoninergic and other neurotransmitter pathways and abnormal cerebello-thalamocortical activity (possibly due to Purkinje cell damage)[10,12] have been proposed in the genesis of cortical myoclonus. The excitation starts in one part of the homunculus and then can spread to another, correlating with a multifocal distribution of the myoclonus in the limbs.[9] Bisynchronous, generalized myoclonus and generalized tonic-clonic seizures may occur when the focal discharge spreads through cortico-cortical and transcallosal pathways.[13]

Cortical myoclonus mainly affects the distal upper limbs and face, reflecting the largest cortical representation of these body areas.[14] It is often focal or multifocal but can be generalized. It is mainly present during the action (though could occur less prominently at rest) and is often induced by somatosensory and less often visual or auditory stimuli.[15] Most patients have both positive and negative myoclonus (NM), which occur either independently of each other or together as a complex. NM occurs when there is a sudden interruption of ongoing muscle contractions. NM can be of subcortical origin as well.[16] Three types of NM have been described: Asterixis in patients with toxic–metabolic encephalopathy, which is a type of subcortical NM[17], NM involving the axial muscles and
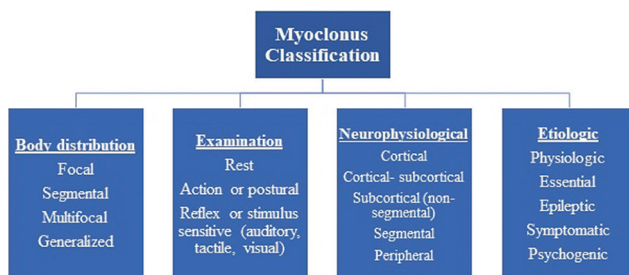

Figure 1: Classification of myoclonus

lower limbs (subcortical origin), resulting in a wobbling gait and sudden falls[18]; and epileptic NM, of cortical origin, in which there is a sudden interruption of tonic muscle activity, time locked to an epileptiform EEG abnormality.

Surface EMG in cortical myoclonus generally shows short duration (<50 ms) burst potentials.[19] Focal, time-locked cortical discharges preceding the EMG activity on EEG-EMG back-averaging is characteristic of cortical myoclonus; the latency is about 20 ms for arm muscles and 30 ms for leg muscles.[2] These EEG discharges are usually lower in amplitude (5–20 uv) than focal epileptiform discharges.[20] SEP shows giant (>10 uv) cortical responses (P27/N35) following normal N20 response; long-latency EMG responses (C reflex) to electrical median nerve stimulation are enhanced (40–45 ms).[21,22] These findings are neither uniformly present nor specific but support the cortical origin of myoclonus.[8] Typical examples of cortical myoclonus are posthypoxic myoclonus ("Lance-Adams syndrome"), progressive myoclonic epilepsies, epilepsia partialis continua, Alzheimer's disease, Creutzfeldt–Jakob disease, corticobasal syndrome, dementia with Lewy bodies, some viral infections, metabolic encephalopathies, and lithium intoxication [Table 1].

Cortical-subcortical myoclonus

It refers to myoclonus arising from paroxysmal abnormal excessive oscillation in reciprocal connections between cortical and subcortical sites, particularly the thalamus.[23,24] This physiology is characteristic of epilepsy syndromes such as juvenile myoclonic epilepsy (JME) and myoclonus with absence epilepsy. Notwithstanding the fact that the subcortical involvement increases the hyperexcitability, it is actually the spread of excitability to the cortical motor centers, which drives the myoclonus event.[8] As the cortical excitability is diffuse, other seizure phenomena, such as altered consciousness, can occur. The jerks are typically generalized, but focal or multifocal jerks also occur. Surface EMG shows myoclonus discharges of 25–100 ms duration. The cortical correlate in EEG shows fast or slow generalized spike/polyspike and wave discharges. Enlarged cortical waves in the SEP can be seen but are not typical. Long latency EMG reflexes are not typically enhanced.[9]

Subcortical nonsegmental myoclonus

The clinical and neurophysiological features of this subtype are more variable than those of cortical and cortical-subcortical subtypes due to multiple possible subcortical sites (between cortex and spinal cord), nuclei, and neuronal circuits from which a burst of excessive activity can originate and be transmitted through descending motor pathways.[8] Simultaneous rostral and caudal recruitment from a subcortical site, reflected in the surface EMG, supports the subcortical origin of myoclonus. Surface EMG shows a burst lasting from 25 to 300 ms, and it is not supported by other electrophysiological cortical correlates (jerk- locked EEG spikes, enlarged cortical SEP waves, or enhanced long latency reflexes). Two major clinical patterns are observed in this subgroup: (1) myoclonus caused by

Table 1: Etiology of cortical myoclonus	
Progressive myoclonic epilepsy and other epileptic syndromes	Lafora body disease
	Unverricht-Lundborg disease
	Neuronal ceroid lipofuscinosis
	Sialidosis (Type I and II)
	Myoclonic epilepsy and ragged red fibers (MERRF)
	Epilepsia partialis continua (e.g. Rasmussen encephalitis)
	Familial cortical myoclonic tremor with epilepsy
Neurodegenerative diseases	Alzheimer's disease
	Creutzfeldt-Jakob disease
	Corticobasal syndrome
	Dementia with Lewy bodies
	Multiple system atrophy
	Huntington's disease (Westphal variant)
	Spinocerebellar degenerations (SCA 2,3,14,19, etc.)
	Progressive myoclonus ataxia syndromes
Infections	Subacute sclerosing pan-encephalitis (SSPE)
	Herpes simplex encephalitis
	Whipple's disease
	Postinfectious encephalitis
Metabolic	Hepatic and renal failure, dialysis syndrome
	Hashimoto's encephalopathy
	Hypoglycemia/nonketotic hyperglycemia/hyponatremia
	Coeliac disease
Drugs	Lithium, tricyclic antidepressants, and methyl bromide
Focal CNS damage	Poststroke
	Post-trauma
	Neoplasia

simultaneous rostral and caudal recruitment of muscle segments along the neuraxis from a localized source—includes brainstem reticular reflex myoclonus, startle as well as startle syndromes and propriospinal myoclonus, and (2) multifocal myoclonus in hereditary essential myoclonus (myoclonus-dystonia).[14]

Brainstem reticular reflex myoclonus

Brainstem reticular myoclonus is generated from the lower brainstem reticular formation in the medulla. It presents with generalized, synchronous jerks that predominantly involve axial and proximal flexor muscles of limbs.[25] These jerks are present at rest and aggravated by voluntary movements. The most striking clinical feature is sensitivity to multisensory stimuli, particularly auditory. Clinically, it can be differentiated from hyperekplexia by the presence of spontaneous myoclonus (at rest) and being stimulus sensitive to tactile stimuli delivered to the distal extremities in contrast to the mantle area.[5] The characteristic electrophysiological feature in multichannel EMG is early activation of muscles supplied by the cranial accessory nerve (sternocleidomastoid and trapezius) followed later by the spread in a rostro-caudal fashion to involve the muscles of the face, limbs, and trunk.[26] These discharges can be brief but are usually more than 100 ms in duration. Reticular reflex myoclonus is seen in hypoxic

encephalopathy, uremia, viral encephalitis and demyelinating, neoplastic, or vascular lesions of the brainstem.[27]

Startle and Startle syndromes

Startle is a physiological brainstem reflex, which is defined as abrupt, involuntary, rapid body jerking following a sudden, unexpected stimulus (e.g., loud noise).[28] It is present in normal healthy individuals starting from 6 weeks of age, and it persists throughout life. It is generated from bulbopontine reticular formation of the lower brainstem, particularly the nucleus reticularis caudalis pontis (nRCP).[29] Clinically, the jerk begins with a blink and facial grimacing followed by bisynchronous flexion of the neck, trunk, elbows, hips, knees, abduction and flexion of the shoulder, and pronation of forearms.[30] This is followed by a period of decreased activity (250–300 ms), and then a late voluntary behavioral (anger, disgust, etc.) and autonomic response that lasts for ≥3–10 seconds. It typically habituates within 1–5 trials of auditory stimuli. EMG activity begins in bilateral orbicularis oculi (within 20–50 ms) followed by involvement of the face, neck, trunk, and limb muscles in a rostro-caudal fashion.[31] When the startle is abnormal, exaggerated, and doesn't habituate to repetitive stimuli, then it is called startle syndrome. The startle syndromes are divided into three broad categories: hyperekplexia, stimulus-induced disorders, and neuropsychiatric disorders.[32] Hyperekplexia (major form) is clinically characterized by three cardinal clinical symptoms: generalized stiffness at birth, exaggerated startle response, and generalized prolonged stiffness after a startle.[31] This major form of hyperekplexia is usually familial secondary to mutations (both dominant and recessive) in the alpha1 subunit of glycine receptor (*GLRA1*; 60% of cases), glycine transporter-2 (*SLC6A5*) (20%–25% of cases), the beta subunit of glycine receptor (*GLRB*) (15%), gephyrin (*GPHN*), or *ARHGEF9*.[33] The minor form is usually sporadic, which presents later and is not accompanied by generalized stiffness. These are usually late-onset cases with hyperekplexia as the sole manifestation.[34] The symptomatic form of hyperekplexia is due to underlying cerebral or brainstem lesions (e.g. brainstem encephalitis, vascular lesions, multiple sclerosis, posthypoxic, neurodegenerative, etc.).[35,36] Startle can occur as a manifestation in other disorders (such as startle epilepsy, stiff person syndrome, strychnine poisoning, etc.) or as a part of neuropsychiatric syndromes (e.g. Latah, Jumping Frenchman, anxiety disorders, and Tourrete syndrome).[32] The electrophysiological difference between exaggerated startle and brainstem reticular myoclonus is efferent conduction time, which is slower in the former as compared to the latter.[37]

Propriospinal myoclonus

It was first described by Brown and colleagues in 1991. It originates from a spinal generator, more commonly at the thoracic cord level, and then recruits the axial muscles up and down in a bidirectional fashion via long polysynaptic propriospinal pathways.[38] It occurs more commonly in middle-aged men, characterized by axial flexion (> extension) jerks involving the neck, trunk, knees, and hips and could occur at a frequency of 1–6 Hz.[5] It usually occurs spontaneously,

typically in a lying down position and can be stimulus sensitive to tapping of the abdomen or eliciting tendon reflexes. It may also occur during the wake-sleep transition.[39] In contrast to brainstem reticular reflex myoclonus, it spares facial muscles and is insensitive to auditory stimuli. EMG burst begins in the rectus abdominis muscle and it ranges from 100 to 5000 ms.[40] Three types of propriospinal myoclonus are described: idiopathic, symptomatic, and functional.[39] Approximately 80% of cases remain idiopathic. Recently, an increasing number of cases with functional etiology has been reported. Symptomatic cases are secondary to spinal cord trauma, infection, tumor, and myelitis.[41]

Hereditary essential myoclonus

It is inherited in an autosomal dominant manner with variable penetrance. Almost 50% of clinically suspected cases are due to mutation in the *epsilon-sarcoglycan (SGCE)* gene on chromosome 7q21.[42] It is classically inherited from the father because of maternal genomic imprinting. The typical age of onset is in the 1st decade with a fairly benign course. Major features include "lightning-like" multifocal action-induced myoclonic jerks involving the upper extremity, neck, and trunk (also present spontaneously).[43] It is usually associated with dystonia in the same distribution as myoclonus in half of the cases. The clinical spectrum also includes psychiatric disorders such as social phobia, obsessive-compulsive disorder, anxiety, depression, and alcohol dependence.[44,45] Myoclonic jerks are dramatically responsive to alcohol. It is increasingly being considered as a neurodevelopmental circuit disorder involving an abnormal neural network comprising the basal ganglia, brainstem, and cerebellum.[46,47] EMG discharges are more than 100 ms in duration, and EEG doesn't show the cortical correlate. SEP and long-latency reflexes are normal.[48]

Segmental myoclonus

In segmental myoclonus, the generator in the brainstem or spinal cord produces movements at that particular segment or few close contiguous segments, giving the jerks a focal or circumscribed distribution. It is unaffected by supraspinal influences like state of consciousness (it persists in sleep), voluntary action (therefore present at rest), and sensory stimulus.[49] Palatal myoclonus (now palatal tremor) is the most common type followed by spinal segmental myoclonus.

Palatal myoclonus (Now recognized as "palatal tremor")

This entity was referred to as palatal myoclonus until 1990 when it was renamed as "palatal tremor" at the first International Congress of Movement Disorders largely due to the rhythmic nature of jerks. It consists of slow (1–4 Hz), rhythmic contraction of the soft palate, sometimes synchronously affecting muscles of the eye, face, tongue, larynx, and even trunk and intercostal muscles.[50] There are two types: essential and symptomatic palatal tremor (SPT). Essential palatal tremor (EPT) represents a heterogeneous disorder as the origin and underlying cause mostly remain elusive. EPT can be classified into isolated primary (unknown cause) and isolated secondary EPT (such as palatal tic, special

skill, and psychogenic). Several studies have suggested a functional etiology in many patients of EPT.[51,52] The oscillator responsible for SPT resides in inferior olivary nuclei. It occurs due to disruption within the Guillain–Mollaret triangle, comprising connections between the dentate nucleus, red nucleus, and inferior olivary nucleus (through superior cerebellar peduncle and central tegmental tract).[50] Important causes of SPT are brainstem vascular lesions, infections, trauma, tumor, or demyelination. Another well-recognized cause of SPT is progressive ataxia palatal tremor syndrome (PAPT). PAPT syndrome may be familial or sporadic. Some familial cases are due to *GFAP* mutations, which cause adult-onset Alexander disease[53] and others due to *FTL1* (ferritin light chain) gene mutations, responsible for autosomal dominant neuroferritinopathy.[54]

Spinal segmental myoclonus

It is confined to muscles innervated by one or a few contiguous spinal segments. Jerks are characteristically rhythmic (1–3 Hz) or semi rhythmic, spontaneous (at rest) and are occasionally stimulus sensitive.[20] It occurs due to the loss of inhibitory interneurons in the dorsal horn of the spinal cord, which produces abnormal oscillations. These oscillations are transmitted to anterior horn cell neurons in corresponding myotomes leading to their spontaneous bursting.[55,56] EMG discharge duration varies between 50 and 1000 ms and is not accompanied by any electrophysiological cortical correlate. It is usually secondary to underlying structural spinal cord pathologies such as myelitis, syringomyelia, spinal cord trauma, vascular lesions, or malignancy.[57]

Peripheral myoclonus

It is characterized by rhythmic or semi-rhythmic focal jerks due to a lesion in the nerve, plexus, or root. The best example is a hemifacial spasm. EMG shows marked discharge to discharge variability in duration and appearance in a given muscle.[58] The duration of these discharges may range from 50 to 200 ms or longer. Central relay mechanisms play a significant role in addition to ectopic excitation and ephaptic transmission resulting from nerve injury.[59]

ETIOLOGICAL CLASSIFICATION

The main categories under this classification scheme are physiologic, essential, epileptic, symptomatic, and psychogenic myoclonus. Each category consists of diverse etiologies of myoclonus.

Physiological myoclonus

It refers to myoclonic jerks occurring in healthy people. It is commonly noticed by a concerned observer such as a spouse. It produces minimal or no disability, and examination is usually normal. The examples of physiological myoclonus are as follows:
a. Hypnic jerks
b. Hiccough
c. Exercise and anxiety-induced
d. Physiological startle response
e. Benign infantile myoclonus with feeding

Essential myoclonus

In essential myoclonus, myoclonus is either the most prominent or the only symptom. The clinical presentation is usually chronic and follows a stable course over time with minimal or no disability.[49] There is no other neuroaxis involvement or cognitive dysfunction. It may be sporadic or hereditary. Sporadic (or idiopathic) essential myoclonus is a heterogeneous entity regarding its distribution and exacerbating factors.[60] Some cases have a false-negative family history and represent hereditary forms.[49]

Epileptic myoclonus

It refers to conditions in which myoclonus occurs in the setting of epilepsy. Myoclonus can occur as one component of the whole seizure (fragments of epilepsy), the only seizure manifestation (myoclonic seizure), or as one of the multiple seizure types within an epileptic syndrome [Table 2].[14] The most typical example of epileptic myoclonus is juvenile myoclonic epilepsy. It represents generalized epilepsy, and myoclonus is often generalized but not necessarily symmetrical.[61] Myoclonic seizures occurring in a primary generalized epileptic syndrome exhibit cortical-subcortical physiology, while those occurring in a secondary generalized epileptic syndrome exhibit cortical physiology.

Symptomatic myoclonus

It is the most common etiological type of myoclonus. It occurs in the context of an underlying medical or neurological illness.[7] Myoclonus is commonly accompanied by other neurological manifestations such as seizure, encephalopathy, ataxia, Parkinsonism, cognitive impairment, spasticity, or peripheral neuropathy. Symptomatic myoclonus is usually cortical. However, subcortical types, such as brainstem reticular myoclonus can also occur.[7] The common etiologies

Table 2: Etiology of epileptic myoclonus[1]

Fragments of epilepsy
  Isolated epileptic myoclonic jerks
  Rasmussen encephalitis and other causes of epilepsia partialis continua
  Idiopathic stimulus sensitive myoclonus
  Photosensitive myoclonus
  Eyelid myoclonia with absence seizures
  Myoclonic- tonic-clonic/myoclonic-atonic seizures
Myoclonic epilepsy syndromes
  Benign myoclonic epilepsy of infancy
  Infantile spasms (West syndrome)
  Severe myoclonic epilepsy of infancy (Dravet syndrome)
  Lennox-Gastaut syndrome
  Myoclonic astatic epilepsy (Doose syndrome)
  Cryptogenic myoclonus epilepsy (Aicardi syndrome)
  Juvenile myoclonic epilepsy (JME)
  Familial cortical myoclonic tremor with epilepsy
Progressive myoclonic epilepsy
  Unverricht-Lundborg syndrome
  Myoclonic epilepsy with ragged red fibers (MERRF)

include posthypoxic myoclonus, myoclonus secondary to neurodegenerative diseases, storage diseases, infections and immune-mediated disorders, metabolic disorders, focal nervous system damage [Table 3], and drugs and toxins [Table 4].

Psychogenic myoclonus

It may occur spontaneously or following an external trauma. Characteristic features include sudden onset and remission, constantly changing anatomical and temporal patterns, distractibility, variable amplitude, inconsistency over time, and placebo response. It can be focal, segmental, multifocal, or generalized.[62] It is aggravated by stress and anxiety, and there is exaggerated stimulus sensitivity to visual or auditory stimuli. Despite these characteristics, it is very difficult at times to differentiate psychogenic from organic myoclonus. EEG-EMG polygraphy helps in differentiating these two. The short duration EMG burst of myoclonus (<75 ms) is impossible to produce voluntarily and so a burst of shorter duration than this strongly suggests organic myoclonus. EEG recording shows classical premovement potential (Bereitschaftspotential) just before the jerk, but its absence doesn't rules out the diagnosis of psychogenic myoclonus.[63]

Table 3: Etiology of symptomatic myoclonus[1]	
Storage diseases	**Immune-mediated/Paraneoplastic**
Lafora body disease	Hashimoto's encephalopathy steroid. responsive autoimmune thyroiditis (SREAT)
Neuronal ceroid-lipofuscinosis	Anti- N-methyl D-aspartate
Sialidosis	(NMDA) receptor encephalitis
GM2 gangliosidosis (Late infantile, juvenile)	Anti-LGi-1 and CASPR2 encephalitis
Tay-Sachs disease	Stiff person syndrome (also paraneoplastic; anti-Hu, Ri antibodies)
Gaucher's disease type III	Progressive encephalomyelitis with rigidity and myoclonus (PERM)
Krabbe's disease	Opsoclonus-myoclonus ataxia syndrome
Action myoclonus renal failure syndrome	Coeliac disease
Spinocerebellar degenerations	**Metabolic**
Progressive myoclonus ataxia syndromes	Hepatic and renal failure, dialysis syndrome
Friedreich's ataxia, ataxia-telangiectasia	Hyperthyroidism
SCAs (SCA 2,3,14,17)	Hyponatremia, hypoglycemia, nonketotic hyperglycemia
	Metabolic acidosis/alkalosis
	Hypoxia
	Vitamin E deficiency
	Mitochondrial disorders
	Biotin deficiency, multiple carboxylase deficiency
Basal ganglia degenerations	**Focal nervous system damage**
Corticobasal degeneration	Vascular (ischemia, hemorrhage)
Huntington's disease (HD)	Tumor
Dentatorubropallidoluysian atrophy (DRPLA)	Post-thalamotomy
Multiple system atrophy (MSA)	Trauma
Torsion dystonia (DYT-*TOR1A*)	Demyelination (e.g. multiple sclerosis)
Neurodegeneration with brain iron accumulation (NBIA)	The peripheral nervous system (trauma, tumor, hematoma)
Wilson's disease	
Parkinson's disease	
Progressive supranuclear palsy (PSP)	
Dementias	**Physical encephalopathies**
Alzheimer's disease	Heatstroke
Dementia with Lewy bodies	Electric shock
Creutzfeldt-Jakob disease	Decompression injury
Frontotemporal dementia	
Infectious or post-infectious	**Multiple system degenerations**
SSPE	Allgrove syndrome
Herpes simplex encephalitis (HSV)	DiGeorge syndrome
Arbovirus encephalitis	Angleman syndrome
HIV, HTLV-I	Familial cortical myoclonic tremor with epilepsy
Postinfectious encephalitis	
Progressive multifocal leukoencephalopathy (PML)	
Whipple disease	
Malaria, syphilis, cryptococcus	
Lyme disease	
Encephalitis lethargica	
Drugs and toxins [Table 4]	**Idiopathic (familial or sporadic)**

Table 4: Drugs and toxins causing myoclonus

Antibiotics (penicillin, cephalosporins, carbapenems, quinolones)

Antidepressants (tricyclic antidepressants (TCAs), serotonin reuptake inhibitors (SSRIs), monoamine oxidase (MAO) inhibitors, lithium), benzodiazepine withdrawal

Antipsychotics (Typical and atypical; tardive myoclonus)

Anesthetic drugs (propofol, midazolam, lidocaine, fluranes)

Antiepileptic drugs (phenytoin, carbamazepine, lamotrigine, pregabalin, gabapentin, phenobarbitone, vigabatrin, primidone)

Anti-Parkinsonian drugs (L-dopa, bromocriptine, amantadine, selegiline)

Antihypertensive and anti-arrhythmic drugs (Ca^{2+}channel blockers such as verapamil and diltiazem; amiodarone)

Narcotics (Morphine, fentanyl, tramadol)

Contrast media

Anticancer drugs (Chlorambucil, busulphan, cyclophosphamide, ifosfamide)

Toxins (Alcohol, aluminum, bismuth, manganese, mercury, methyl bromide, dichlorodiphenyltrichloroethane)

EVALUATION OF PATIENTS WITH MYOCLONUS

Evaluation is divided into a simple three-step approach.

Step 1: History and examination with determination of clinical classification

The first critical step in evaluation is a thorough history and physical examination. Important aspects in history are age of onset, mode of onset (acute, subacute, or chronic), progression (static or progressive), precipitating and relieving factors, associated symptoms (seizures, cognitive decline, ataxia, dystonia, etc.), and family history.[5] Events coincident with the onset of myoclonus are important clues, including a recent introduction of any new medication/s and comorbid medical conditions.

Age at onset helps in deciding the major etiological classification category. For example, onset in infancy or childhood along with seizures, ataxia, and/or cognitive decline suggests epileptic myoclonus. Acute-subacute onset myoclonus is seen in various metabolic disorders such as liver and renal failure, electrolyte disturbances, thyrotoxicosis, some neuro infections [herpes simplex virus (HSV), arbovirus, Lyme disease], posthypoxia, vascular lesions (stroke or hemorrhage), post-traumatic, drug- and toxin-induced myoclonus, autoimmune/inflammatory, and paraneoplastic disorders. A more chronic progressive course is characteristic of neurodegenerative diseases, progressive myoclonic epilepsy syndromes, and other genetic epilepsy syndromes.[9]

Family history is equally important to narrow down the differential diagnosis. Autosomal recessive transmission is seen in various progressive myoclonus epilepsy (PME) syndromes and metabolic disorders (e.g., Gaucher's disease, Wilson's disease, GM1 gangliosidosis, neurodegeneration with brain iron accumulation (NBIA), etc., while dominant inheritance is seen in myoclonus-dystonia, spinocerebellar ataxias, Huntington's disease (HD), dentatorubral pallidoluysian atrophy (DRPLA), and familial cortical tremor. Mitochondrial

inheritance is seen in myoclonic epilepsy with ragged red fibers (MERRF).

The examination of a patient with myoclonus should focus on the following parameters:
1. Body distribution (focal, segmental, multifocal, axial, or generalized)
2. Activation pattern (spontaneous, on voluntary action, stimulus sensitive)
3. Temporal profile (continuous v/s intermittent, rhythmic v/s irregular)
4. Other neurological signs (ataxia, dystonia, Parkinsonism, eye movement abnormalities, etc.)

After a comprehensive history and physical examination, one should be able to define the etiological classification of myoclonus (physiological, essential, epileptic, or symptomatic). This helps in narrowing down the clinical possibilities and avoiding unnecessary investigations. A simple clinical approach to myoclonus is depicted in Figure 2.

Step 2: Basic laboratory testing

The basic laboratory testing for etiological workup of myoclonus includes the following:

Renal and liver function tests

Blood glucose

Electrolytes (including calcium, magnesium)

Thyroid function tests and thyroid antibodies

Drug and toxin screening (if clinical suspicion)

EEG

Brain and spine imaging [computed tomography (CT) or magnetic resonance imaging (MRI)]

Infection workup (hemogram, urine analysis, chest X-ray, lumbar puncture, blood culture) if signs of fever, encephalopathy

These steps help in defining the etiology of myoclonus in most cases. If the basic tests do not reveal the diagnosis, more advanced testing should be considered. It includes

Genetic testing (specific or whole-exome sequencing)

Neuronal antibodies (including paraneoplastic)

CSF examination

Specific toxins or enzyme assays

Tissue biopsy

Step 3: Neurophysiological testing

Neurophysiological testing is an underutilized tool in the diagnosis of various movement disorders. It helps in differentiating myoclonus from other jerky hyperkinetic movement disorders such as chorea, tics, dystonia, and tremor, in those situations where clinical differentiation is difficult.[64] It helps in determining the physiological classification of
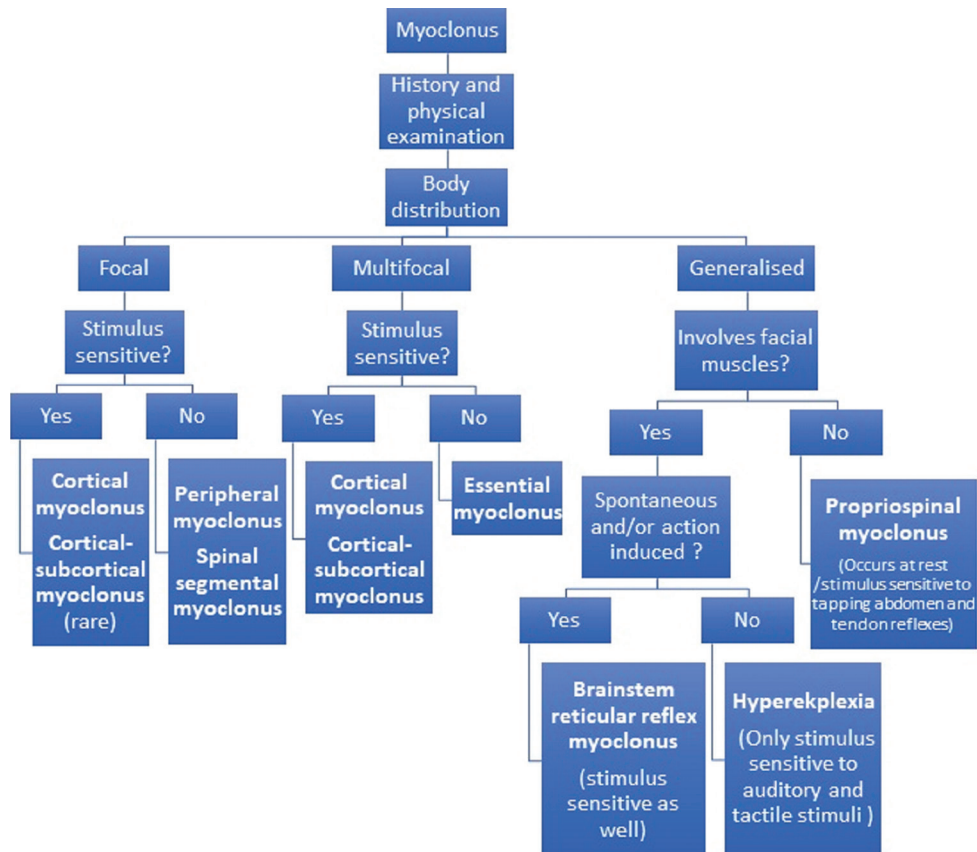
Figure 2: A clinical approach to physiological classification of myoclonus

myoclonus (cortical, cortical-subcortical, subcortical, or peripheral) and gives clues to anatomical localization and etiology, and guiding treatment strategies. Electrophysiology can also differentiate between the central and peripheral origin of jerky movements.[65] The basic testing includes surface EMG, EEG-EMG polygraphy, jerk-locked EEG back averaging, SEP, and long-latency cortical reflex (C-reflex). The surface EMG demonstrates the brief muscle bursts characteristic of positive myoclonus, and the silent period of negative myoclonus.[2] EEG-EMG (with back averaging) should be usually performed first, preferably recording multiple muscles (including pairs of agonist-antagonist muscles). Similarly, EEG should be recorded using multiple electrodes placed over the sensorimotor cortex, supplemental motor area, and midline (Cz, C1, and C2).[64] SEP and C-reflex are useful for identifying the cortical correlate of the myoclonus.[66]

Based on the burst duration, the pattern of spread, and conduction velocity of efferent volley, electrophysiological testing helps in identifying the physiology of myoclonus.[64] Cortical and brainstem reticular reflex myoclonus have short duration EMG bursts (usually <50 ms; can be up to 100 ms in brainstem myoclonus) and faster conduction velocity (> 50 m/s in the brainstem and >100 m/s in cortical myoclonus). On the other hand, startle reflex, spinal segmental, and propriospinal myoclonus show longer burst duration (>100 ms; up to a few seconds in spinal myoclonus) and slower conduction velocity (slowest in propriospinal myoclonus).[64]

Functional myoclonus is characterized by longer duration EMG bursts (>100 ms) and the presence of premovement Bereitschaftspotential. Common electrophysiological findings of different physiological types of myoclonus are illustrated in Table 5.

TREATMENT OF MYOCLONUS

The most important factor in the management of myoclonus is the treatment of underlying etiology (e.g., removal of offending drug/s or toxin/s, correction of metabolic or electrolyte disturbances, excision of surgically treatable brain or spinal lesions, immunotherapy for immune-mediated or paraneoplastic syndromes, and treatment of underlying malignancy). However, symptomatic treatment is usually required as the treatment of the underlying disorder is insufficient in the majority of cases.[14]

The best strategy for symptomatic treatment is to define the physiological classification of myoclonus with the help of neurophysiological test/s because different drugs act in different physiological types of myoclonus.[67] Moreover, a drug useful in one physiological type may not work in another type of myoclonus or may even worsen it. All drugs should be started at a low dose followed by gradual increment considering the potential side effects (e.g., sedation, worsening of cognition, ataxia). If the physiological classification of myoclonus cannot be determined, presuming the physiology

Table 5: Electrophysiological characteristics of different myoclonus subtypes				
Type of myoclonus	Surface EMG burst durations (ms)	EEG correlates (back averaging)	SEP (P27/N35 response)	Long latency reflex
Cortical myoclonus	< 50 (usually<30)	Present	Enlarged	Enhanced
Cortical-subcortical myoclonus	25-100	Present	Can be enlarged (not always)	Normal
Brainstem reticular reflex myoclonus	25-300 (usually<50 ms)	Absent	Normal	Normal
Startle reflex	50-100	Absent	Normal	Normal
Spinal segmental myoclonus	50-1000	Absent	Normal	Normal
Propriospinal myoclonus	100-5000 (usually 150-450 ms)	Absent (Bereitschaftspotential can be present)	Normal	Normal
Peripheral myoclonus	50-200	Absent	Normal	Normal
Psychogenic myoclonus	Usually>100	Characteristic premovement potential (Bereitschaftspotential)	Normal	Normal

of myoclonus that occurs in suspected etiology is the best way to proceed. If both the etiological diagnosis and physiology of myoclonus are unclear, the drugs that work in cortical myoclonus should be tried first as it is the most common type of myoclonus.[8] Recommendations for symptomatic treatment are mostly based on case reports and small case series, and controlled evidence for the same is very sparse.

Cortical myoclonus

Drugs used for cortical myoclonus act by facilitating inhibitory GABAergic transmission and/or reducing the hyperexcitability in the sensorimotor cortex. Usually, a combination of drugs is required for the control of cortical myoclonus. The four most effective agents are levetiracetam, piracetam, valproic acid, and clonazepam. Levetiracetam and valproic acid are the first-line agents. Levetiracetam[68,69] and piracetam[70,71] both reduces cortical hyperexcitability by binding to synaptic vesicle protein 2A (SV2A) as well as modulating Ca^{2+} and K^+ currents. Few small case studies have proven levetiracetam and piracetam to be very useful in cortical myoclonus. Levetiracetam is initiated at 500–1000 mg daily in two divided doses followed by a gradual titration up to a maximum dose of 3000 mg. The daily dose of piracetam ranges from 2.4 gm to 24 gm per day in three divided doses. Evidence from uncontrolled observational studies suggests that valproic acid is also effective for cortical myoclonus.[72,73] It acts by increasing the synthesis and decreasing the degradation of GABA. It also reduces excitability by altering ion conductance. The therapeutic dose range is 1200–2000 mg daily in two to three divided doses. Clonazepam is also useful in cortical myoclonus.[74] It should be introduced slowly from 0.5 mg daily and titrated gradually up to the maximum dose of 5 mg/day (rarely up to 12 mg). An abrupt dose reduction or withdrawal of any of these agents can precipitate a withdrawal seizure or worsen myoclonus. Other effective agents are zonisamide,[75] sodium oxybate,[76] brivaracetam,[77] and primidone. Medications such as phenytoin, carbamazepine, oxcarbazepine, lamotrigine, gabapentin, pregabalin, and vigabatrin aggravate the cortical myoclonus and are usually avoided.[67] Gait disturbances secondary to negative myoclonus and asterixis are usually difficult to treat and are most resistant to treatment.

Cortical-subcortical myoclonus

The drug of choice for this subtype is valproic acid, particularly in juvenile myoclonic epilepsy (JME).[78] The therapeutic dose range is 500–2000 mg daily in two to three divided doses. If it is not effective or contraindicated, levetiracetam[79] and lamotrigine[80] can be used. Lamotrigine can occasionally aggravate myoclonic seizures. Other adjuncts that can be useful are ethosuximide, topiramate, and clonazepam.

Subcortical-nonsegmental myoclonus

Standard antiepileptic drugs used in cortical myoclonus are not helpful in most types of subcortical-nonsegmental myoclonus.[67] Clonazepam is the first choice in most subtypes such as brainstem reflex myoclonus, hyperekplexia, myoclonus-dystonia, and propriospinal myoclonus. Apart from GABAergic mechanisms, serotonergic and cholinergic mechanisms also play a role in the pathogenesis of brainstem reflex myoclonus. Based on this, 5-hydroxytryptophan has been tried with success in brainstem reflex myoclonus.[81] Zonisamide (100–300 mg/day),[82] sodium oxybate,[83,] and anticholinergics can be used as alternative agents for myoclonus-dystonia. Medication refractory myoclonus of myoclonus-dystonia also responds to bilateral pallidal deep brain stimulation.[84] For propriospinal myoclonus, other effective agents are zonisamide and levetiracetam.[85]

Segmental myoclonus
Palatal tremor

Treatment of palatal tremor is difficult. Many drugs have been tried as "off label" to date with only limited success. The list of possibly useful drugs includes clonazepam, baclofen, carbamazepine, sumatriptan,[86] lamotrigine, phenytoin, piracetam, anticholinergics, and tetrabenazine. Botulinum toxin has been proven to be safe and effective, but it is technically difficult to inject.[87] Surgical procedures such as tensor veli palatini tenotomy and eustachian tube occlusion can be considered for disabling ear clicking.

Spinal segmental myoclonus

The drug of choice in this subtype is usually clonazepam (up to 6 mg/day), but complete suppression is uncommon. Botulinum toxin sometimes alleviates associated pain and movements of spinal segmental myoclonus.[88] Alternative options include levetiracetam, carbamazepine, and tetrabenazine.[57]

Peripheral myoclonus

Both clonic movements and tonic spasms of hemifacial spasm respond excellently to botulinum toxin injection.[89] Medications such as carbamazepine and gabapentin[90] can be tried but have limited benefit. Microvascular decompression is a good treatment option, but it is reserved for botulinum toxin treatment–refractory patients.[91]

Conclusions and Future Directions

Myoclonus is a clinical sign that can be seen in a wide variety of disorders. A comprehensive history and detailed neurological examination are key for the pragmatic evaluation of myoclonus and defining the etiology. Neurophysiological testing helps in identifying the presumed physiology of myoclonus. Both underlying etiology and the presumed physiology helps in establishing the best treatment strategy. In the majority of cases, the treatment remains unsatisfactory, so more controlled therapeutic trials are needed in the future. More research is required into the mechanism of myoclonus generation, and this may lead to better pharmacological options. Increased availability of advanced genetic testing may lead to the discovery of new genes associated with myoclonus.

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