Myoclonus

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

PURPOSE OF REVIEW: **This article offers clinicians a strategic approach for making sense of a symptom complex that contains myoclonus. The article presents an evaluation strategy that highly leverages the two major classification schemes of myoclonus. The goal of this article is to link evaluation strategy with diagnosis and treatment of myoclonus.**

RECENT FINDINGS: **The growth of medical literature has helped better define myoclonus etiologies. Physiologic study of myoclonus types and etiologies with electrophysiologic testing has provided greater clarity to the pathophysiology of the myoclonus in various diseases. Although studies have been limited, the role of newer treatment agents and methods has made progress.**

SUMMARY: **Myoclonus has hundreds of different etiologies. Classification is necessary to evaluate myoclonus efficiently and pragmatically. The classification of myoclonus etiology, which is grouped by different clinical presentations, helps determine the etiology and treatment of the myoclonus. The classification of myoclonus physiology using electrophysiologic test results helps determine the pathophysiology of the myoclonus and can be used to strategize symptomatic treatment approaches. Both basic ancillary testing (including EEG and imaging) and more comprehensive testing may be necessary. Treatment of the underlying etiology is the ideal approach. However, if such treatment is not possible or is delayed, symptomatic treatment guided by the myoclonus physiology should be considered. More controlled study of myoclonus treatment is needed. Further research on myoclonus generation mechanisms should shed light on future treatment possibilities.**

INTRODUCTION

Myoclonus is defined as a sudden, brief, lightninglike muscle contraction.[1] Myoclonus may occur from an increase in contraction activity (positive myoclonus) or inhibition of contraction activity (negative myoclonus).[1] To recognize the visual appearance of a myoclonic jerk, the clinician should consider the quickest movement that can be performed with that body part. Indeed, the brief movement of myoclonus does not slow down, pause, or "hang up." Dystonic spasms or dyskinetic jerks may be sudden, but they are not lightning brief. A tremor discharge may be brief but does not result in a jerk or sudden movement. Indeed, the myoclonus phenotype is both a jerk (sudden) and the most transient (brief) compared with any other movement disorder

CITE AS:
CONTINUUM (MINNEAP MINN) 2019;25(4, MOVEMENT DISORDERS): 1055–1080.

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RELATIONSHIP DISCLOSURE:
Dr Caviness reports no disclosure.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Caviness discusses the unlabeled/investigational use of anticholinergic medications, botulinum toxin, carbamazepine, clonazepam, deep brain stimulation, levetiracetam, sodium oxybate, and tetrabenazine for the treatment of myoclonus.

phenotype. Although this definition has been quoted for decades, a study found only moderate agreement on labeling a movement as myoclonus when presented with a mixture of myoclonus, tics, and psychogenic jerks.[2]

The incidence of myoclonus in the clinic setting is estimated at 1.3 cases per 100,000 person-years, with a prevalence of 8.6 cases per 100,000 in the overall population.[3] These numbers are probably an underestimate because myoclonus is most often secondary to another disorder. However, no single etiology or even a small group of etiologies accounts for most of the cases. Indeed, myoclonus has a bewildering number of types and etiologies.

To efficiently evaluate a patient with an unknown etiology for myoclonus, clinicians must have an organized approach to myoclonus evaluation. Fortunately, an efficient and pragmatic strategy exists to best define the diagnosis, physiology, and treatment approach for a specific myoclonus case. Central to this strategy are myoclonus classification schemes. Myoclonus has popular classification schemes based on clinical presentation and etiology and a separate scheme based on physiology.[1,4]

This article first covers the overall evaluation strategy for myoclonus. Second, the physiologic classification of myoclonus is discussed. Next, clinical presentation and etiologic classification and myoclonus types are reviewed. Finally, symptomatic treatment strategies are discussed. This article focuses on the connection between the evaluation (including classification) and symptomatic treatment of myoclonus.

AN EFFICIENT AND PRAGMATIC EVALUATION OF MYOCLONUS

The evaluation is organized into three steps.

Step One: History and Examination With Clinical Presentation Classification

A comprehensive history and examination are the critical first steps. Events coincident or close to the myoclonus onset are important clues, including comorbid medical conditions. For example, the starting of a new medication may implicate that medication as the myoclonus etiology. A subacute onset of the myoclonus should trigger a targeted evaluation of infectious/postinfectious, inflammatory/immune, paraneoplastic, and toxic-metabolic etiologies. Chronic onset of diffuse or multifocal myoclonus is commonly caused by neurodegenerative and genetic etiologies. Chronic onset of focal myoclonus can suggest a neoplastic etiology. A family history of myoclonus may suggest a genetic cause, including epileptic syndromes. A history of concomitant symptoms, especially neurologic symptoms, is important to document.

The examination should characterize the amplitude, distribution, and activation characteristics of the myoclonus because various etiologies may have typical examination findings. Thus, the examination may be used to corroborate the etiology of the myoclonus. Equally important is the documentation of the involvement of other neurologic signs. For example, dementia commonly implicates a cortical disease. Moreover, myoclonus in a patient with dementia is likely to have a cortical physiology. Myoclonus commonly occurs in a variety of neurodegenerative disorders, so the history and physical examination may define the overall diagnosis (eg, multiple system atrophy, corticobasal syndrome, dementia with Lewy bodies). A similar concept can be appreciated with ataxic, parkinsonian, dystonic, and even peripheral disorders.

After the comprehensive history and physical examination, the clinical presentation classification of myoclonus should occur as described below, ie, physiologic, essential, epileptic, or symptomatic. Such classification can then guide further evaluation by allowing the clinician to narrow the diagnostic possibilities under the clinical classification category.

Step Two: Basic Ancillary Testing

Ancillary testing of a patient with myoclonus is recommended if the myoclonus etiology is not determined with a comprehensive history and physical examination. Even if an etiology is suspected, basic testing is useful in confirming that common or easily treatable etiologies are ruled out. The following basic testing for myoclonus should be considered:

- Electrolytes (including calcium and magnesium)
- Glucose
- Renal and hepatic function tests
- Drug and toxin screen (including bismuth)
- EEG
- Brain imaging (eg, CT, MRI, functional imaging)/other imaging

This testing evaluates for basic electrolyte and metabolic disorders known to cause myoclonus. Although a metabolic etiology may present in the outpatient clinic, metabolic and drug causes are particularly relevant in the hospital setting. Moreover, myoclonus may appear after initial hospitalization because new medications and progression of medical problems commonly occur during the hospital course.

EEG should be performed in all cases of myoclonus unless the myoclonus etiology is obvious since myoclonus most commonly arises from either cortical or cortical-subcortical physiology, including seizures. The EEG also constitutes the first step in the electrophysiologic evaluation of the myoclonus. For more electrophysiologic definition, adding surface EMG channels to the EEG or performing multichannel recording by using an EMG machine is recommended.

As discussed in the section on the physiologic classification of myoclonus, the EMG discharge duration and pattern of myoclonus provide more exact physiologic classification of the myoclonus.

Consideration of brain imaging is recommended, especially for symptomatic presentations. If the distribution of myoclonus could be consistent with a segmental or peripheral physiology or with propriospinal (nonsegmental) myoclonus, then spinal cord or peripheral imaging, or both, should be considered.

The combination of these two steps will lead to the etiology of the myoclonus in most cases. Moreover, if non–myoclonus signs and symptoms are present, then appropriate evaluation for a unifying diagnosis should be undertaken. Only after that evaluation should more comprehensive testing for the suspected etiology of the myoclonus be undertaken.

Step Three: More Comprehensive Testing if Needed

If the above testing does not reveal the etiology of myoclonus, then other testing may be required. Further testing should be strongly guided by the evaluation

KEY POINTS

- The brief, lightninglike muscle contraction defines it as myoclonus.
- Myoclonus is a symptom or sign, not a diagnosis. It occurs in multiple diseases and conditions.
- Evaluation for myoclonus begins with a comprehensive history and neurologic examination that allows the clinical presentation classification into a physiologic, essential, epileptic, or symptomatic category.
- EEG should be the initial electrophysiologic testing for myoclonus without a determined etiology.

results of steps one and two. Because myoclonus is caused by so many potential etiologies, considering the best diagnosis when taking into account the nonmyoclonus clinical features and all test evidence may be useful. To define the physiology of the myoclonus, more electrophysiologic testing may be needed.

The list of eligible tests for more comprehensive testing is vast, which reinforces the need for a targeted strategy and, ideally, a stepwise evaluation if numerous tests are being considered. The broad categories of additional testing may include specific genetic tests, whole exome sequencing, neuronal specific antibodies (including paraneoplastic), additional specific toxins, and CSF examination, among others.

CLASSIFICATION OF MYOCLONUS PHYSIOLOGY BY USING ELECTROPHYSIOLOGIC TEST RESULTS

Physiologic classification requires testing in a clinical neurophysiology laboratory. Modern digital EMG and EEG have the capability to allow for different testing modes (eg, multichannel surface EMG recording) and the use of extra (or substituted) positions for EEG with EMG recordings or vice versa. Individual cases need tailored testing, and the neurophysiologist should be comfortable with interpretation.

In this scheme, the classification focuses on the pathophysiologic genesis of the myoclonus, regardless of its clinical presentation. Indeed, different myoclonus physiologies exist within the same clinical presentation classification category and may be cortical, subcortical, or segmental. Also, myoclonus may have the same physiology (eg, segmental) but a different anatomical location (eg, brainstem or spinal cord). Thus, physiologic information is complementary and not redundant to the clinical presentation classification. The determination of physiology category is based on findings from electrophysiologic tests. Because symptomatic treatment strategy closely parallels the abnormal physiology being treated, the combination of both clinical and physiologic classification gives the clinician a strategy for treatment of myoclonus.[4]

The physiologic classification of myoclonus is outlined below with basic electrophysiologic test findings of the major categories. Methodologies and complete description details are available.[5]

Cortical Myoclonus

The classification of cortical myoclonus implies that intrinsic cortical hyperexcitability is the major driver of the genesis of the patient's myoclonus. The abnormally excessive motor cortical activity occurs at any one instant in a relatively small part of the motor homunculus. The excitation occurs in one part of the homunculus, then in another, usually correlating with a multifocal distribution of the myoclonus in the limbs. However, excitability spread is common, subsequently activating adjacent muscles almost synchronously or even bilateral muscles bisynchronously when the discharge transmits through the corpus collosum. Myoclonus EMG discharges are brief (25 ms to 100 ms) in duration and usually spread to antagonist and other contiguous muscle groups (FIGURE 8-1A).

Chronic posthypoxic myoclonus (Lance-Adams syndrome) is a well-known type of cortical myoclonus. The myoclonus in disorders classified as progressive myoclonus epilepsy such as Unverricht-Lundborg disease and mitochondrial conditions are classically cortical. Neurodegenerative illnesses affecting the

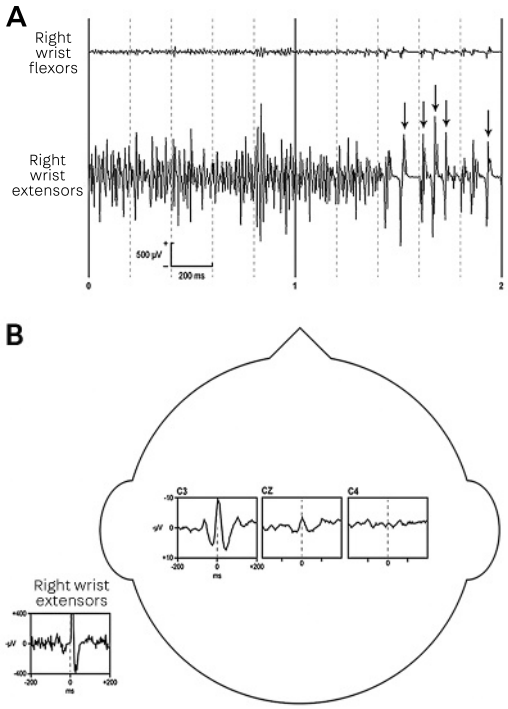

FIGURE 8-1

Electrophysiology of cortical myoclonus from a patient with dementia with Lewy bodies. *A,* Surface EMG polygraphy of right wrist muscles showing myoclonus EMG discharges (*arrows*). Note the brief-duration myoclonus EMG discharges. *B,* EEG showing back-averaged correlate maximal over the left central scalp region in the C3 EEG electrode. The averaged trigger EMG waveform is in the lower left corner.

cortex, such as Alzheimer disease and dementia with Lewy bodies, commonly have cortical myoclonus. Certain drugs, such as lithium, will have myoclonus that is cortical.

EEG may show epileptiform activity correlating with the myoclonic EMG discharges, either grossly or with back averaging. If this is demonstrated, cortical myoclonus is confirmed.[6] EEG-EMG back averaging can show a cortical correlate even if no EEG discharge is grossly apparent on the EEG (FIGURE 8-1B). Supportive evidence for a cortical physiology may include enlarged cortical waves in the somatosensory evoked potential (FIGURE 8-2A) and enhanced long-latency EMG reflexes to peripheral nerve stimulation (FIGURE 8-2B).

Cortical-Subcortical Myoclonus

This myoclonus physiology occurs with primary generalized seizures, such as myoclonic seizures in juvenile myoclonic epilepsy and myoclonus associated with absence seizures. Generalized spike-and-wave discharges on EEG that correlate with the myoclonus confirm this category of physiology.[7,8] The abnormal excessive neuronal activity is spread between cortical and subcortical circuits, producing the diffuse excitation. As such, this physiology is dissimilar from localized cortical myoclonus and thus is in a different physiology category. Because this excitation over the sensorimotor cortex is simultaneously widespread, the myoclonus is commonly generalized. Myoclonus EMG discharges are brief (25 ms to 100 ms). Enlarged cortical waves in the somatosensory evoked potential can be seen but are not typical. Enhanced long-latency EMG reflexes are not associated with this physiology of myoclonus.

Subcortical/Nonsegmental Myoclonus

Two major patterns are seen in subcortical/nonsegmental myoclonus. In the first pattern, the initial myoclonus EMG discharge corresponds to the subcortical nidus level (at the brainstem or spinal cord) followed by simultaneous rostral and caudal recruitment spread of muscle involvement. One example is brainstem reticular myoclonus in which the first discharge arises in the cranial nerve XI brainstem innervated muscles (trapezius and sternocleidomastoid). As the

KEY POINTS

- **Cortical myoclonus physiology is best defined by brief (<50 ms) EMG discharges and a focal EEG correlating with the myoclonus. Enlarged cortical somatosensory evoked potential wave, abnormal long-latency EMG reflex, and increased corticomuscular coherence are supportive but not confirmatory.**
- **Cortical-subcortical myoclonus physiology is best defined by generalized epileptiform discharges that occur with the myoclonus. It most commonly takes the form of EEG generalized spike-and-wave discharges.**

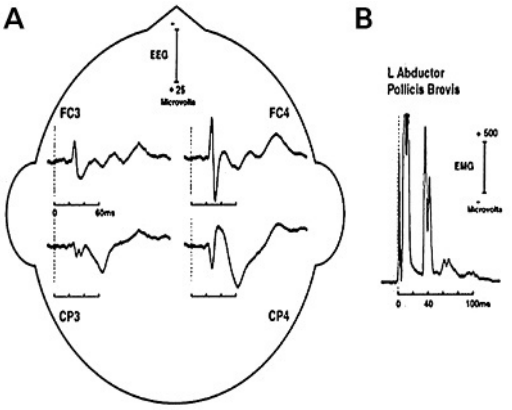

FIGURE 8-2
Electrophysiologic exaggerated reflex features in cortical myoclonus due to Huntington disease. Many cases of cortical myoclonus will show electrophysiologic evidence of exaggerated responses to somatic stimulation. This is believed to be hyperexcitability in cortical sensory areas that parallels the hyperexcitability in cortical motor areas. *A,* Enlarged cortical somatosensory evoked potential. *B,* Enhanced long-latency EMG reflex from median nerve stimulation averaged with rectified (absolute value) signal. Note that the averaged discharges after 50 ms are of abnormally long latency. FC3/FC4 (frontocentral) and CP3/CP4 (centroparietal) refer to the standard 10-20 EEG electrode positions.
Modified with permission from Caviness JN.[5]

excitation spreads rostrally, cranial nerve VII (facial) and then V (masseter) muscles jerk. At the same time, the caudally spreading excitation recruits bilateral arm muscles and then leg muscles, thereby producing their jerking. Trunk muscles activate progressively in the caudal direction. To the observer, the jerk is generalized. These discharges can be brief but more often are more than 100 ms in duration. Another example is propriospinal myoclonus, which has its nidus in the cervical or thoracic spinal cord and then a similar bidirectional muscle recruitment up and down the spinal muscle segments.[9] The myoclonus type may be caused by a variety of spinal lesions, or it may occur during sleep transition.

In the second subcortical/nonsegmental myoclonus pattern, myoclonus EMG discharges are also longer than 100 ms in duration, but a multifocal pattern is observed. The myoclonus in myoclonus-dystonia is an example of this pattern, and the electrophysiologic findings have been classically defined by Roze and colleagues.[10] In both patterns, EEG shows no consistent correlate, and usually the EEG is unremarkable. Somatosensory evoked potential and long-latency EMG reflexes are normal.

Segmental Myoclonus

In segmental myoclonus the myoclonus EMG discharges usually last longer than 100 ms and are highly rhythmic. By definition, the discharges are limited to a few contiguous segments of the brainstem or spinal cord.[11] The discharges are either simultaneous with the other segments or at least time locked. The discharges are fairly persistent and not usually affected by stimuli or exogenous factors. Palatal segmental myoclonus is the most common location of segmental myoclonus. Palatal segmental myoclonus is divided into essential and symptomatic clinical types.[12] Different types of focal lesions of the spinal cord can cause spinal segmental myoclonus.[12]

Peripheral Myoclonus

The term *peripheral myoclonus* should be reserved for instances where the movement phenotype is myoclonus, although it may coexist with other phenotypes as well. However, the distribution is defined by one or more peripheral nervous

system elements (eg, root, nerve). Myoclonus EMG discharges have a variable duration and appearance in a given muscle.[13] The duration of these discharges may range from 50 ms to 200 ms or longer. Often discharges are simultaneous or time locked between muscles in the same peripheral nerve distribution. Needle EMG may prove extremely useful in demonstrating the discharges within small muscles of the same peripheral nerve distribution as well as differential diagnosis of the movement itself (eg, myokymia). The mechanism of peripheral myoclonus is controversial in many cases.[14] Although association with a peripheral nervous system lesion is found, central reorganization of motor pathways may be a required event for peripheral myoclonus to occur.[15] However, this is difficult to confirm.

CLASSIFICATION OF MYOCLONUS ETIOLOGY GROUPED BY CLINICAL PRESENTATION

In this classification scheme, the etiologies of myoclonus are organized around the clinical presentation. In the mid-20th century, comprehensive reviews of myoclonus showed that etiologies of myoclonus were associated with certain clinical circumstances. This concept was used in the long-established clinical classification scheme of Marsden and colleagues[1] (TABLE 8-1). The main categories in this classification scheme are physiologic, essential, epileptic, and symptomatic. Each category reflects the elements of characteristic syndrome presentations, and the various etiologies listed below each category most closely fit with the clinical presentation reflected by that category. The list of etiologies in TABLE 8-1 has been modified to reflect current literature.

Physiologic Myoclonus

Physiologic myoclonus refers to myoclonic jerks that occur as normal phenomena, and they occur in almost all people. This myoclonus may occur with different frequency and prominence among normal individuals and may not even be noticed when it occurs. Physiologic myoclonus is commonly noticed by a concerned observer, such as a spouse. Jerks occurring in sleep or sleep transition are common examples (CASE 8-1).[16] Normal startle response and hiccups are also physiologic myoclonus examples. However, it should be realized that some phenotypes of physiologic myoclonus may be part of a clinical syndrome or disorder. In these instances, clinical symptoms are caused by the myoclonus being disruptive or excessive. A prime example is hyperekplexia, in which an otherwise normal startle response is nonfatigable and symptomatic. As such, hyperekplexia is considered a pathologic disorder.

Essential Myoclonus

The clinical presentation of essential myoclonus is characterized by a chronic and relatively stable course in which myoclonus is a prominent or the only symptom. The jerks interfere with coordination and may become moderate, but the patient usually compensates without disability (CASE 8-2).[17] Nonmovement neurologic systems are usually not affected, but they occur in some patients.[18]

HEREDITARY. Myoclonus-dystonia syndrome is the most cited example of hereditary essential myoclonus.[10] As the name indicates, the coexistence of myoclonus and dystonia is characteristic, although the relative proportion of myoclonus and dystonia is variable. Autosomal dominant genetic transmission

KEY POINTS

- Subcortical-nonsegmental myoclonus physiology is defined by one of two patterns: (1) initiation from the brainstem or spinal cord followed by simultaneous rostral and caudal EMG recruitment or (2) multifocal myoclonus EMG discharges. Both patterns show EMG discharges of more than 100 ms.
- Segmental myoclonus physiology is defined by low-frequency rhythmic myoclonus EMG discharges that persist almost continuously, with more than 100 ms duration EMG discharges confined to a few contiguous muscle segments.
- Peripheral myoclonus physiology is defined by a highly variable myoclonus EMG discharge duration confined to a specific root, plexus, or peripheral nerve.
- Physiologic myoclonus is a normal phenomenon. Education and reassurance are usually the best treatments.

TABLE 8-1 **Classification of Myoclonus Etiology Grouped by Clinical Presentation[a,b]**

Physiologic Myoclonus (Normal Phenomenon, Healthy Individuals)

- 1 Sleep-associated myoclonus (eg, hypnic jerks)
- 2 Anxiety induced
- 3 Exercise induced
- 4 Hiccup (singultus)
- 5 Benign infantile myoclonus with feeding
- 6 Startle reflex

Essential Myoclonus (Primary Symptom, Mild or Nonprogressive History)

- 1 Hereditary (myoclonus-dystonia syndrome, autosomal dominant)
- 2 Sporadic

Epileptic Myoclonus (Seizures Predominate, Part of Chronic Seizure Disorder)

- 1 Fragments of epilepsy
  - A Focal motor seizures (including epilepsia partialis continua)
  - B Myoclonus patterns within a seizure
    - i Myoclonic-tonic-clonic
    - ii Myoclonic-atonic
    - iii Atonic
  - C Isolated epileptic myoclonic jerks
  - D Idiopathic stimulus-sensitive myoclonus
  - E Photosensitive myoclonus
  - F Myoclonus during absence seizures
    - i Petit mal epilepsy
    - ii Eyelid myoclonia
- 2 Myoclonic seizures
  - A Infantile spasms
  - B Myoclonic astatic epilepsy (Lennox-Gastaut syndrome)
  - C Cryptogenic myoclonus epilepsy (Aicardi syndrome)
  - D Myoclonic epilepsy
    - i Infancy
    - ii Early childhood
    - iii Juvenile
    - iv Adult

Symptomatic Myoclonus (Secondary, Progressive, or Static Encephalopathy Predominates)

- 1 Progressive myoclonic epilepsy syndromes
  - A Lafora body disease
  - B GM2 gangliosidosis (late infantile, juvenile)
  - C Tay-Sachs disease

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- **D** Gaucher disease (noninfantile neuronopathic form)
- **E** Krabbe leukodystrophy
- **F** Ceroid lipofuscinosis (Batten disease)
- **G** Sialidosis (cherry-red spot) (types 1 and 2)
- **H** Unverricht-Lundborg disease (Baltic myoclonus disease)
- **I** Action myoclonus-renal failure syndrome

2 Spinocerebellar degenerations

- **A** Idiopathic progressive myoclonic ataxia (dyssynergia cerebellaris myoclonica [also known as Ramsey Hunt syndrome])
- **B** Friedreich ataxia
- **C** Ataxia-telangiectasia
- **D** Other spinocerebellar degenerations

3 Basal ganglia degenerations

- **A** Wilson disease
- **B** Torsion dystonia
- **C** Neurodegeneration with brain iron accumulation (NBIA)
- **D** Progressive supranuclear palsy
- **E** Huntington disease
- **F** Parkinson disease
- **G** Multiple system atrophy
- **H** Corticobasal degeneration
- **I** Dentatorubral-pallidoluysian atrophy

4 Dementias

- **A** Creutzfeldt-Jakob disease
- **B** Alzheimer disease
- **C** Dementia with Lewy bodies
- **D** Frontotemporal dementia
- **E** Rett syndrome

5 Inflammation (infectious, postinfectious, antibody-mediated, paraneoplastic)

- **A** Opsoclonus-myoclonus syndrome
  - **i** Idiopathic
  - **ii** Paraneoplastic
  - **iii** Infectious
  - **iv** Other
- **B** Subacute sclerosing panencephalitis
- **C** Encephalitis lethargica
- **D** Arbovirus encephalitis

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- **E** Herpes simplex encephalitis
- **F** Human T-lymphotropic virus I
- **G** HIV
- **H** Miscellaneous bacteria (streptococcus, clostridium, other)
- **I** Malaria
- **J** Syphilis
- **K** Cryptococcus
- **L** Lyme disease
- **M** Progressive multifocal leukoencephalopathy
- **N** Antibody-mediated
  - **i** Anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis
  - **ii** Voltage-gated potassium channel antibody (LGI1 and CASPR2)
- **O** Paraneoplastic encephalopathies

6 Metabolic

- **A** Hyperthyroidism
- **B** Hepatic failure
- **C** Renal failure
- **D** Dialysis syndrome
- **E** Hyponatremia
- **F** Hypoglycemia
- **G** Nonketotic hyperglycemia
- **H** Multiple carboxylase deficiency
  - **I** Biotin deficiency
- **J** Mitochondrial dysfunction
- **K** Hypoxia
- **L** Metabolic alkalosis
- **M** Vitamin E deficiency

7 Toxic and drug-induced syndromes (see TABLE 8-2)

8 Physical encephalopathies

- **A** Posthypoxia (acute and chronic [Lance-Adams syndrome])
- **B** Posttraumatic
- **C** Heat stroke
- **D** Electric shock
- **E** Decompression injury

9 Focal nervous system damage

- **A** Central nervous system
  - **i** Poststroke

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- ii Postthalamotomy
- iii Tumor
- iv Trauma
- v Inflammation (eg, multiple sclerosis)
- vi Moebius syndrome
- vii Developmental

B Peripheral nervous system

- i Trauma
- ii Hematoma
- iii Tumor/infiltration

10 Malabsorption

A Celiac disease

B Whipple disease

11 Eosinophilia-myalgia syndrome

12 Exaggerated startle syndrome

A Hereditary

B Sporadic

13 Hashimoto encephalopathy (steroid-responsive encephalopathy associated with autoimmune thyroiditis [SREAT])

14 Multiple system degenerations (genetic disorders not falling into another category)

A Allgrove syndrome

B DiGeorge syndrome

C Angelman syndrome

D Familial cortical myoclonic tremor and epilepsy

15 Primary progressive myoclonus of aging

16 Myoclonus associated with sleep

A Generalized

B Propriospinal

17 Unknown

HIV = human immunodeficiency virus; LGI1 = leucine-rich glioma inactivated protein 1; CASPR2 = contactin-associated proteinlike 2.

[a] Modified with permission from Marsden CD, et al, Movement Disorders.[1] © 1982 Butterworths.

[b] The genetics and clinical details of these etiologies are complex and are not given in detail.

occurs, and onset is usually early. ε-Sarcoglycan mutations are known to be associated with this syndrome, but other genes are also involved.[19] The clinical spectrum of these mutations is complex. Other clinical symptoms have been reported for some patients, and some patients with myoclonus-dystonia have little or almost insignificant myoclonus. Psychiatric symptoms may be significant, but other symptoms vary markedly between families.

SPORADIC. Cases of sporadic essential myoclonus are very heterogeneous with regard to clinical characteristics, including timing, distribution, and exacerbating factors among other examination findings. Sporadic essential myoclonus likely includes heterogeneous yet undiscovered etiologies of myoclonus and instances of false-negative family history.

Epileptic Myoclonus

Epileptic myoclonus occurs in syndromes that are traditionally considered to be epilepsy (ie, a chronic seizure disorder).[7] In most instances, the myoclonus is the seizure itself and is called a *myoclonic seizure*. Less commonly, the

CASE 8-1

A 53-year-old man presented for evaluation of whole-body jerks. He was accompanied by his wife, who reported that her spouse sometimes had violent whole-body jerks as he was falling asleep. These may have been going on for years but seemed more apparent recently. He had recently been diagnosed with diabetes mellitus, and his wife was worried that these jerks were related to his diabetes mellitus. His current medications were insulin, losartan, atorvastatin, and aspirin. The patient denied trouble with falling asleep, insufficient sleep, or excessive daytime somnolence. He had no other neurologic concerns, and his examination was normal. His EEG was normal.

He was diagnosed with hypnic jerks presenting as physiologic sleep myoclonus. The patient and his wife were told that this jerking was of no concern at that time. They were instructed to return to clinic if any jerks were disrupting his sleep or preventing her from sleeping. Reassurance was given that this is a normal phenomenon that varies in occurrence and size among the healthy population.

COMMENT

The patient in this case has myoclonus symptoms characteristic of the physiologic clinical presentation category. Myoclonus occurs normally in humans. In this patient, no disabling or functional consequence accompanied the myoclonus. In fact, from the standpoint of the patient, the myoclonus was asymptomatic. There was no connection to the diagnosis of diabetes mellitus or any medication that the patient was taking. It is typical that the patient or patient's family expresses concern about the myoclonus and its possible associations. The evaluation should be guided by associated symptoms, the neurologic examination, and plausible differential diagnosis. The EEG was ordered to rule out seizures, since such generalized jerks may be epileptic in nature.

myoclonus is just one component of the whole seizure manifestation and is called a *fragment* of the seizure or epileptic syndrome. An example of this is when eyelid myoclonus occurs with an absence seizure. As phenomena related to seizures, these myoclonic jerking episodes are most often paroxysmal and unpredictable (CASE 8-3).

Juvenile myoclonic epilepsy is the most common and typical example of an epileptic myoclonus syndrome.[8] It represents generalized epilepsy, and the myoclonic seizure produces the jerk. The myoclonus is most often generalized

CASE 8-2

A 24-year-old woman presented with a history of "jerking as far back as I can remember." She experienced bilateral jerking of the arms with muscle activation and random jerks of the neck. Although these movements were bothersome, she related only mild disability with using her hands and arms for handwriting, eating, and other hand movements. She reported no other symptoms. Rare alcohol consumption decreased the jerking. She had been previously diagnosed with essential tremor, and the patient was being treated with propranolol with modest effect. The patient was adopted, her family history was unknown, and she worked as a graduate student.

Her examination revealed myoclonic continuous small-to-moderate multifocal jerking in random directions occurring unpredictably in bilateral proximal upper extremities during muscle activation. A slight left torticollis was present. Postural activation of the left arm showed mild hyperpronation of the forearm. The rest of the examination was normal.

Laboratory evaluation showed no electrolyte disturbance or other toxic-metabolic or inflammatory abnormality. Imaging and EEG were normal.

She was diagnosed with myoclonus-dystonia syndrome presenting as essential myoclonus (classified as subcortical-nonsegmental physiology). Propranolol was discontinued with only a mild detrimental effect, and clonazepam 1 mg twice daily decreased the myoclonic jerking by more than 50% per patient report.

COMMENT

Some patients, like the one described here, can have repetitive rhythmic myoclonic movements of the upper limbs resembling the postural tremor of essential tremor. The fact that the myoclonus was the primary symptom and was chronic with little disability makes essential myoclonus the correct clinical classification category. The reference to myoclonus-dystonia means that both myoclonus and dystonia coexist in the patient. However, in some cases, there may be mostly myoclonus or mostly dystonia. Although no genetic testing was done, an ε-sarcoglycan or another gene mutation could have been found in this patient. However, currently, such genetic testing would not affect treatment, although it affords a more exact diagnosis and possible future treatment implications. If symptoms become severe and not adequately controlled with medication (see the section on treatment for subcortical myoclonus), deep brain stimulation could be considered.

but may not be perfectly symmetrical. Although often occurring in the early morning hours, the seizures arise unpredictably regardless of the muscle state, relaxation, or activation. Other types of generalized seizures (eg, tonic-clonic) are common in patients with juvenile myoclonic epilepsy. There may be photosensitivity and predisposing factors such as sleep deprivation, alcohol use, and other stresses.

Symptomatic Myoclonus

This category comprises the most common clinical presentation category and the largest list of myoclonus etiologies.[3] In this category, myoclonus is secondary to a medical or neurologic illness. Seizures may be a significant part of the patient's illness, but the seizure is not the major myoclonus phenotype as in epileptic myoclonus. Other neurologic systems are typically affected and may

CASE 8-3

A 57-year-old woman presented for evaluation of episodes of left arm jerking. The patient stated that these symptoms had occurred for decades as sporadic jerking episodes lasting a few seconds. Recently, they were occurring as a series of repetitive jerks occurring for 15 to 45 seconds on most days. These episodes were unpredictable, and the jerks disabled the use of the arm while they were occurring. She reported no other symptoms. Her past medical history revealed no known history of seizures, and her family history was unremarkable.

Her examination was unremarkable except for a witnessed jerking spell characterized by abrupt repetitive moderate-to-large myoclonus of the left arm, at a frequency of about a 1 time per second. Multiple muscles were involved. After several seconds, the jerks became less frequent and abruptly stopped.

Her laboratory evaluation was normal. Imaging was normal. Interictal EEG findings were normal, but EEG during a jerking spell showed rhythmic, sharply contoured theta activity occurring over the right central head region.

She was diagnosed with focal motor seizures presenting as epileptic myoclonus (cortical physiology). She was treated with carbamazepine, resulting in nearly complete remission of the jerking episodes.

COMMENT

These episodes presented as unpredictable myoclonus from rest and likely represented focal motor seizures with epileptic myoclonus as the correct clinical presentation classification category. The lack of an interictal EEG abnormality should not dissuade a clinician from a seizure diagnosis. The gross EEG cortical correlate during a jerking episode confirmed a cortical physiology for this myoclonus. It is important to define the electrophysiologic pattern as much as possible. Because these were focal seizures, carbamazepine was a reasonable treatment option in this patient; however, it should be noted that myoclonic seizures with generalized spike and wave may become worse with carbamazepine. This highlights the importance of distinguishing myoclonus etiologies within the epileptic myoclonus category with assistance from the EEG pattern.

involve cognition, parkinsonism, ataxia, sleep dysfunction, autonomic symptoms, upper motor neuron findings, and even peripheral nerve dysfunction. Almost all the major medical pathophysiologic processes can include myoclonus as a symptom, including metabolic, degenerative, toxic, structural lesion, infectious, and inflammatory (CASE 8-4).

PROGRESSIVE MYOCLONIC EPILEPSY SYNDROMES. Various storage diseases fall under the clinical syndrome of progressive myoclonic epilepsy.[22] Progressive myoclonic epilepsy is a chronic, progressive, neurologic syndrome that manifests as some combination of myoclonus, seizures, ataxia, and dementia. These disorders usually affect younger individuals and are often fatal. Several clinical differences exist between individual storage diseases in their age of onset, rate of progression, details of clinical expression, and other clinical manifestations. The neuropathology in the brain is widespread. Genetic testing is used for an increasing number of etiologies.

NEURODEGENERATION. Myoclonus occurs in chronic degenerative disorders, including spinocerebellar disorders, basal ganglia disorders, and dementing diseases. The syndrome dyssynergia cerebellaris myoclonica (also known as Ramsey Hunt syndrome) refers to an idiopathic progressive myoclonic ataxia.[23] Progressive myoclonic ataxia can appear similar to progressive myoclonic epilepsy, but progressive myoclonic ataxia involves ataxia more than the seizures that are seen in progressive myoclonic epilepsy. A variety of progressive myoclonic conditions have been noted to have a predominant progressive myoclonic ataxia rather than progressive myoclonic epilepsy phenotype.[24] Thus, distinguishing between a progressive myoclonic epilepsy and progressive myoclonic ataxia phenotype can assist with differential diagnosis.

Cortical myoclonus occurs across the spectrum of Lewy body disorders.[25] The myoclonus in Parkinson disease is small amplitude and may be confused with tremor.[26] In dementia with Lewy bodies, the myoclonus is larger and occurs in about 58% of patients.[27] The myoclonus that occurs in patients with dementia with Lewy bodies is more likely to occur at rest than the myoclonus in Parkinson disease.

Multiple system atrophy manifests as varying degrees of parkinsonism, ataxia, and autonomic dysfunction. In the parkinsonian presentation, postural activation triggers small-amplitude myoclonus in about 36% of patients, whereas a stimulus-induced myoclonus to touch or muscle stretch is not uncommon in the cerebellar presentations.[28]

Myoclonic jerks, both action and stimulus sensitive, commonly occur in corticobasal degeneration. The reported range of the prevalence of myoclonus in corticobasal degeneration is wide but previously thought to occur in the majority of clinical cases. However, an autopsy series yielded 27%, suggesting a smaller occurrence in pathologically confirmed cases.[29] The distribution of the myoclonus in corticobasal degeneration is either asymmetric or focal and is similar in distribution to the other clinical manifestations of the disease.

Myoclonus occurs in about 43% of patients with Alzheimer disease.[27] The usual appearance is small multifocal distal jerking, but widespread or generalized jerks may be present. Myoclonus is a hallmark of Creutzfeldt-Jakob disease and

KEY POINTS

- Essential myoclonus is pathologic but chronic with little or no disability. It is not common.
- Epileptic myoclonus etiologies are chronic seizure disorders that have myoclonus as a prominent phenomenon.
- Symptomatic myoclonus is secondary to another disorder, neurologic or non-neurologic. Multiple other symptoms and signs are usually present or tied to definable pathology.

CASE 8-4

A 76-year-old man presented for evaluation of symptoms of myoclonus and confusion that he had experienced over the past few months. His past medical history included hypertension, diabetes mellitus controlled by diet, and back surgery. His social history revealed no smoking and only occasional alcohol use. He was a farmer and ran his farm with his children, who had become concerned about his bizarre behavior, confusion, and involuntary movements. A referral was made to neurology with concerns about a diagnosis of Creutzfeldt-Jakob disease.

On examination, he was awake and alert, but he was disoriented to location and time. He scored poorly on a short test of mental status. Multifocal mild-to-moderate myoclonus in all four extremities was present at rest and was markedly exacerbated with muscle activation. Quick stretching of his right thumb evoked a local, mild myoclonic jerk. No reflex sensitivity was present. His gait was moderately unsteady. The remainder of the neurologic examination was unremarkable.

Laboratory testing showed no electrolyte disturbance or other toxic-metabolic abnormalities, and there was no evidence of infection or inflammation.

Brain imaging was unremarkable, and EEG demonstrated significant generalized slowing; no sharp waves or any epileptiform abnormality was present. No gross EEG correlate was seen during elicited myoclonus. Movement neurophysiology revealed short-duration (<50 ms) myoclonus surface EMG discharges that were synchronous between agonist, antagonist, and contiguous muscle groups. EEG back averaging of 108 rectified (absolute value) signal myoclonus EMG discharges yielded a time-locked cortical transient 22 ms before the averaged myoclonus EMG discharge. Somatosensory evoked potential showed no enlarged cortical components. Abnormal long-latency EMG reflexes were not present. A paraneoplastic blood panel showed significantly elevated voltage-gated potassium channel complex antibodies.

The patient was diagnosed with autoimmune encephalitis secondary to voltage-gated potassium channel complex antibodies presenting as symptomatic myoclonus. Treatment with a 5-day course of methylprednisolone 1 g IV/d yielded a dramatic improvement in myoclonus as well as his cognitive status.

COMMENT

The subacute onset and presence of abnormal mental status suggest that this patient's presentation was consistent with symptomatic myoclonus as the correct clinical presentation classification category. Antibodies to the voltage-gated potassium channel complex include the subtypes leucine-rich glioma inactivated protein 1 (LGI1) and contactin-associated proteinlike 2 (CASPR2). Such antibodies may cause multiple neurologic syndromes.[20] It should be realized that this syndrome may present similarly to Creutzfeldt-Jakob disease, but once discovered, it may be treatable with immunosuppressive therapy.[21] In this case, the patient responded to treatment of the autoimmune encephalitis, and no symptomatic treatment of the myoclonus was necessary.

can occur with rest, voluntary muscle activation, or stimuli.[30] When the myoclonus in Alzheimer disease is large and widespread, it may be confused with Creutzfeldt-Jakob disease.

Various syndromes of frontotemporal dementia had an overall cumulative prevalence of myoclonus of 23% in one series.[27] An idiopathic progressive syndrome with cortical action myoclonus as the main symptom has been described in older individuals as *primary progressive myoclonus of aging*.[31] The clinical course resembles a chronic neurodegenerative syndrome, but the cause is unknown.

INFLAMMATION. Opsoclonus-myoclonus syndrome presents with subacute opsoclonus (irregular, rapid eye movements) and multifocal or generalized myoclonus.[32] Opsoclonus-myoclonus in adults may be due to an infectious, autoimmune, paraneoplastic, or drug-induced etiology.

Neuroblastoma is a major paraneoplastic etiology consideration in children with opsoclonus-myoclonus. In adults, a wider variety of tumors are associated with paraneoplastic cases (eg, ovarian, lung, breast, kidney). The number of discovered idiopathic autoimmune syndromes with myoclonus and associated antibodies is growing.[33] One example is anti–*N*-methyl-D-aspartate (NMDA) receptor encephalitis, which can be seen in children and adults. Antibodies to the voltage-gated potassium channel complex can be associated with a variety of neurologic presentations, but prominent myoclonus is seen in some cases.[20]

METABOLIC CONDITIONS. Myoclonus often occurs in the hospital setting in patients with metabolic abnormalities, frequently with mental status changes. The myoclonus may be multifocal and subtle or generalized and almost constant as in myoclonic status epilepticus. The prognosis in such cases depends on the severity and reversibility of the underlying metabolic process. Organ dysfunction and electrolyte abnormalities are common acquired metabolic etiologies. Asterixis, which is known as *negative myoclonus*, is a well-known characteristic of toxic and metabolic encephalopathy. It is characterized by brief lapses in postural tone usually observed during postural activation with the patient's arms outstretched and wrists extended and is particularly common in kidney and liver failure.

DRUG-INDUCED. In a patient with myoclonus, all drugs, either in isolation or combination, must be scrutinized for a potential causative role in the myoclonus. Drug-induced myoclonus can be due to a wide variety of agents (TABLE 8-2). This myoclonus is potentially fully treatable because it is almost always reversible on withdrawal of the offending agent or agents. A spectrum of lithium-induced myoclonus exists with regard to different clinical manifestations of motor cortex hyperexcitability. At therapeutic levels or mild lithium toxicity cortical action myoclonus can be associated with a mildly slower EEG background rhythm. Instances of greater lithium toxicity can demonstrate motor seizures and generalized convulsions. Liver or kidney dysfunction may elevate the levels of certain myoclonus-causing drugs or their metabolites, thereby contributing to myoclonus. Withdrawal of certain medications, such as sedatives and anti-seizure agents, may cause myoclonus.

POSTHYPOXIA. Myoclonus is known to occur after hypoxia that is significant enough to cause coma.[35] Acute myoclonus after hypoxia presents as spontaneous or stimulus-triggered generalized jerks. Recent literature has suggested that this myoclonus possibly arises from the brainstem.[36] Chronic posthypoxic myoclonus (Lance-Adams syndrome) occurs after some recovery of mental status.[36] Multifocal action myoclonus dominates the clinical picture. Chronic posthypoxic myoclonus can be present in facial muscles and affect speech and swallowing. Some patients also have cerebellar ataxia and negative myoclonus, which can cause sudden falls. Patients with either acute or chronic posthypoxic myoclonus may also have seizures from the hypoxic damage.

MYOCLONUS TYPES

Certain myoclonus entities have characteristic presentations on examination and are ingrained in the vernacular of clinicians, and have designations that are long ingrained in the literature. These entities may be idiopathic or have variable

TABLE 8-2 **Drug Classes and Examples of Drugs Associated With Myoclonus**[a]

Psychiatric Medications

- Cyclic antidepressants
- Selective serotonin reuptake inhibitors (SSRIs)
- Monoamine oxidase inhibitors
- Lithium preparations
- Antipsychotic agents (including tardive syndrome)

Anti-infectious Agents

- Penicillins
- Carbapenem classes

Narcotics

- Morphine
- Fentanyl

Anticonvulsants

- Phenytoin
- Valproic acid

Anesthetics

- Lidocaine
- Midazolam

Contrast Media

Cardiac Medications

- Antiarrhythmics (eg, amiodarone, flecainide)

Calcium Channel Blockers

[a] Modified with permission from Caviness JN, Brown P, Lancet Neurol.[34] © 2004 Elsevier.

classification, and have distinctive examination findings that are used to coin a term for them. These major myoclonus types are discussed below.

Palatal Myoclonus

The term *palatal myoclonus* coincides with a segmental distribution of and around the soft palate. Expectedly, the physiologic classification is segmental. It is the most common cause of segmental myoclonus and a common cause of myoclonus in general.[3] Some experts prefer the term *palatal tremor*. However, a literature search reveals that *palatal myoclonus* is used in the majority of cases. It is recommended that the determination be based on the phenotypic appearance of the repetitive movement. Some examples do have a very rhythmic and continuous sinusoidal cadence, and it is reasonable to refer to this as *palatal tremor*. For movements that are jerky or somewhat irregular, *palatal myoclonus* is the correct term.

Palatal myoclonus can be due to a variety of etiologies.[37] Essential palatal myoclonus parallels the characteristics of an essential myoclonus clinical presentation. In essential palatal myoclonus, the muscle agonist is the tensor veli palatini, and the myoclonus is frequently associated with an ear-clicking sound, and often disappears with sleep (CASE 8-5). In the more common symptomatic palatal myoclonus, the palatal movement is due to contractions of the levator veli palatini, has other symptoms related to the causative lesion, and is more persistent. Symptomatic palatal myoclonus is believed to arise from disruption within the Guillain-Mollaret triangle, a pathway connecting the red nucleus to the inferior olivary nucleus (central tegmental tract), the inferior olivary nucleus to the dentate nucleus (inferior cerebellar peduncle), and the dentate nucleus to the red nucleus (superior cerebellar peduncle). Essential cases are idiopathic with or without a family history. Symptomatic cases are most often due to a structural lesion (eg, stroke).

Propriospinal Myoclonus

Propriospinal myoclonus was described by Brown and colleagues[9] in 1991. It arises from a subcortical-nonsegmental physiology within the spinal cord in which the trigger then travels rostrally and caudally simultaneously via slow propriospinal pathways. Extension or flexion trunk jerks may occur (CASE 8-6). Cases may be idiopathic, but lesions are common. Multiple reports exist of propriospinal myoclonus occurring during transition into sleep, when waking, or both.[39]

Orthostatic Myoclonus

Orthostatic myoclonus manifests as leg shaking when the patient is standing, similar to orthostatic tremor. In contrast to orthostatic tremor, orthostatic myoclonus produces much more difficulty with gait and has a much higher prevalence of associated neurologic problems.[40] It can be difficult to distinguish between these two orthostatic movement disorders because of significant clinical overlap on history and examination. However, the surface EMG pattern in the lower extremities appears to be different between orthostatic tremor and orthostatic myoclonus. Instead of the rhythmic 13-Hz to 16-Hz surface EMG discharges that are seen with orthostatic tremor, orthostatic myoclonus shows lower frequency and more discharge duration variability with many brief

discharges (<100 ms). A variety of disorders have been associated with orthostatic myoclonus, including Parkinson disease.

Cortical Tremor

The myoclonus type known as cortical tremor was first described in 1990.[41] It has the classic features of cortical physiology, including enlarged cortical somatosensory evoked potentials. However, the myoclonus EMG discharges occur rhythmically or semirhythmically at 6 Hz to 9 Hz, which mimics a nonspecific muscle activation tremor. Cortical tremor can occur from different etiologies. A particular syndrome, familial autosomal dominant cortical tremor, myoclonus, and epilepsy, is now a defined syndrome.[42]

Minipolymyoclonus

Minipolymyoclonus is a form of multifocal myoclonus and is characterized by small jerks in different locations.[43] This term has also been used to describe small-amplitude jerks in patients with spinal muscular atrophy. Hence, the

CASE 8-5

A 33-year-old woman presented because of "an obnoxious sound" in her ears. When it began 5 to 7 years ago, she thought that it was simply "ringing in her ears" from listening to loud music and just a nuisance. Lately, the sounds were distracting her. She had no other symptoms. Her past medical, surgical, and family history were unremarkable.

Examination revealed audible clicking from both ears. Inspection of the soft palate showed that the roof of the soft palate was rhythmically moving. She had no other movements of the mouth, face, or elsewhere. The rest of her neurologic examination was normal. Laboratory testing was unremarkable. Brain MRI was normal. She was diagnosed with essential palatal myoclonus (tremor) presenting as essential myoclonus with a segmental physiology. Treatment with clonazepam was started but did not change the clicks. Botulinum toxin injection into the tensor veli palatini muscle eliminated the clicks.

COMMENT

The clinical course in this patient, without other signs and symptoms and the relative slow progression, was most consistent with the clinical presentation of essential myoclonus. Symptomatic myoclonus begins more abruptly but may be delayed after an acute lesion, nevertheless. In addition, symptomatic palatal myoclonus often involves other areas of the mouth or face. Another distinction is that cases of essential palatal myoclonus have the click as the primary symptom, whereas cases of symptomatic cases mostly have other symptoms from the lesion, such as dysphagia, numbness, and ataxia. Essential palatal myoclonus/tremor usually shows a rhythmic movement that resembles tremor, justifying the label of essential palatal tremor. Evidence in the literature supports botulinum toxin as a viable treatment option.[38] However, the potential risks must be clearly delineated. In many centers, the injection is performed by an otolaryngologist for safety reasons.

evaluation may need to assess for lower motor neuron disorders through needle EMG to distinguish from small myoclonus. It is not exactly clear when myoclonus is small enough to use this term. Hence, it is advisable to avoid using this term all together, describing these jerks as small and multifocal in a certain distribution.

TREATMENT OF MYOCLONUS

The etiology of the patient's disorder should be the most important consideration when deciding on treatment because symptomatic treatment has limitations. If treatment of the etiology is not possible or is delayed, then symptomatic treatment can be considered. Some treatments of myoclonus may worsen cognitive status or movement coordination; therefore, the treatment of myoclonus must be weighed against likely side effects. Moreover, if

CASE 8-6

A 72-year-old woman presented for evaluation of lower thoracic jerking that had slowly increased over many months. These jerks caused her to arch her back and were emanating from her lower thoracic spine. She stated that this caused a very uncomfortable sensation that would run up and down her spine; this sensation was just as unsettling as, if not more than, the movement itself. She had a long history of aching back and neck pain. Her past medical history included hypertension and esophageal reflux.

Examination showed trunk extension myoclonus that was worse when she was sitting than when recumbent or standing. Sensitivity to tactile stimulation in the lower thoracic spine was present but inconsistent. There were no upper motor neuron signs.

Brain and cervical spine MRI and EEG were normal. MRI of the thoracic spine showed a herniated disc at T10 which caused mild edema at that level of the spinal cord.

She was diagnosed with a T10 central herniated disk producing propriospinal myoclonus presenting as symptomatic myoclonus with a subcortical-nonsegmental physiology. The thoracic disk herniation was repaired surgically, and the myoclonus was not present a few weeks after the operation.

COMMENT

Propriospinal myoclonus may have a definable causative lesion in one-third of cases. In this patient, the herniation of the thoracic disk was presumed to have caused the progressive extension jerks of the trunk. The importance of treating the underlying etiology cannot be overemphasized, and this justifies the evaluation to discover that etiology. In this patient, no symptomatic treatment of the myoclonus was necessary in the long term. The patient was treated with clonazepam before the surgery, which resulted in only about 50% improvement and with some sedation. The clonazepam was discontinued postoperatively because the jerks disappeared over a few weeks.

symptomatic treatment is started, therapeutic benefit must be weighed against side effects just after beginning therapy and longitudinally.

It is acknowledged that very little controlled evidence exists for specific symptomatic treatments for myoclonus. Thus, recommendations are based on small studies, case reports, and experience. This is not ideal, and evidence-based reviews become problematic with so few studies reaching criteria for inclusion. Standard titration schedules for these medications can be applied. However, for patients with multiple medical problems and medications, slower titrations may be necessary. The dosages mentioned below are for adults, and dosages may have to be modified with other concomitant medications or liver/kidney dysfunction. Treatment of neuropsychiatric comorbidities, such as depression, should also garner attention. Physical and occupational therapy should be considered within the myoclonus treatment strategy.

The best symptomatic treatment strategy is formulated on the basis of the physiology of the patient's myoclonus.[4] Physiologic classification best predicts symptomatic treatment response to the various antimyoclonus medications. Ideally, electrophysiologic testing is used to define physiology as in the above section. However, if electrophysiologic testing is incomplete or unavailable, then the myoclonus physiology that is typically associated with a defined etiology can be applied. Examples include chronic posthypoxic myoclonus with a presumed cortical physiology, juvenile myoclonic epilepsy with a cortical-subcortical physiology, and segmental pathology and localization associated with a segmental myoclonus physiology. However, if treatment fails, then more definition of the physiology may be useful to better define the treatment strategy. If neither the etiology nor the physiology can be defined, then treatment effect is left to chance and may be more precarious. The following treatment guidelines are discussed under each physiologic classification category.

Cortical Myoclonus

Levetiracetam is usually the first-line treatment of cortical myoclonus. This drug is chemically related to piracetam, an older drug used previously for posthypoxic myoclonus in countries where it was available. Levetiracetam (1000 mg/d to 3000 mg/d divided into 2 daily doses) has shown effectiveness in a few small studies where cortical physiology is present.[44–47] Clonazepam (1 mg/d to 3 mg/d divided into 2 or 3 daily doses) or valproic acid (500 mg/d to 2000 mg/d divided into 2 or 3 daily doses) may be used if levetiracetam is discontinued for any reason or in combinational therapy for myoclonus.[48–50] Sodium oxybate has shown some efficacy in case reports.[51] Brivaracetam, a drug with structural similarity to levetiracetam, has not shown consistent efficacy for cortical myoclonus.[52] Perampanel has shown efficacy in cortical myoclonus, including in a study with 12 patients with Unverricht-Lundborg disease.[53] Initially, deep brain stimulation was met with some skepticism for cortical myoclonus. However, more reported cases with positive results suggest a controlled trial is needed to determine case-based efficacy and the best site for stimulation.[54]

Cortical-Subcortical Myoclonus

The primary generalized epilepsy syndromes that produce myoclonus (eg, juvenile myoclonic epilepsy, absence syndromes) usually receive valproic acid (500 mg/d to 2000 mg/d divided into 2 or 3 daily doses) as the initial antiseizure

drug.[32,55] Besides controlling other seizure manifestations in a generalized epilepsy syndrome, the myoclonus will also respond. Lamotrigine or levetiracetam are agents used when valproic acid is not successful or cannot be given, as in the case of women of childbearing age.[56,57] In rare instances, lamotrigine may worsen myoclonic seizures, so close monitoring is necessary. Brivaracetam may be useful when levetiracetam cannot be tolerated in cortical-subcortical myoclonus.[57]

Subcortical-Nonsegmental Myoclonus

The therapies for this category vary more when compared with either cortical or cortical-subcortical myoclonus and are almost purely based on anecdotal literature evidence. Clonazepam is a good first choice, including reticular reflex myoclonus, myoclonus-dystonia, opsoclonus-myoclonus, and propriospinal myoclonus.[17,34,36,58] Zonisamide (300 mg/d to 500 mg/d divided into 1 or 2 daily doses) and anticholinergics are used as well.[17] It must be emphasized that consistent evidence for efficacy is much less than it is for the agents discussed above in the cortical and cortical-subcortical categories. In myoclonus-dystonia syndrome, the subcortical myoclonus has been known to respond to deep brain stimulation therapy.[59] An experienced center should be consulted if this therapy is considered and the risks and benefits of surgery carefully considered.

Segmental Myoclonus

This physiologic type of myoclonus is notorious for its lack of responsiveness to treatment. Clonazepam and other antiseizure medications are tried most often.[11] For palatal myoclonus, botulinum toxin injections (dosage variable according to muscle) have been reported as effective in some cases.[38] For the ear clicking in essential palatal myoclonus, the tensor veli palatini muscle is injected, but other muscles may be appropriate depending on the symptom targeted. In spinal segmental myoclonus, botulinum toxin therapy may help with the discomfort of the myoclonic muscle contractions.[60] In all these cases, the potential adverse effect of botulinum toxin injections should be carefully considered.

Peripheral Myoclonus

The twitching in hemifacial spasm is the most famous example of peripheral myoclonus. Botulinum toxin injections (dosage variable according to muscle) usually help both the quick phasic contractions as well as the more sustained spasms.[61] Other cases of peripheral myoclonus may respond to botulinum toxin injection.[13] Antiseizure medications, such as carbamazepine, were mostly used before botulinum toxin was available. Such medications can still be tried if botulinum toxin is not preferred in a particular patient.

TRENDS

Three prominent trends in myoclonus should be mentioned. First, an increasing number of myoclonus etiologies that have complex genetics have been discovered and defined. This applies to both established and newly discovered etiologies of myoclonus. At this time, if justified, a targeted search for a genetic basis may be reasonable. In the future, whole genome sequencing may provide the best way to find a variety of genetic etiologies that are difficult to diagnose or confirm otherwise. Electrophysiology is being better defined for more etiologies, presentations, and types of myoclonus. This has driven more rational treatment

KEY POINTS

- A determined etiology for the myoclonus will allow the clinician to decide whether the underlying myoclonus cause is treatable or curable.
- If treatment of the etiology of myoclonus is not possible or is delayed, then symptomatic treatment should be considered if overall improvement is possible when weighing potential side effects.
- Symptomatic treatment best aligns with the myoclonus physiology classification. An agent that suppresses a specific myoclonus physiology can potentially do that for all myoclonus cases with that common physiology.
- Cortical myoclonus treatments are also antiseizure agents and are able to reduce the hyperexcitability of the cortex, resulting in suppression of cortical myoclonus.
- Subcortical myoclonus agents operate at the subcortical movement areas such as the basal ganglia and brainstem.
- Deep brain stimulation has been used successfully for the myoclonus-dystonia syndrome.
- Botulinum toxin injections have been used for segmental and peripheral myoclonus.

strategies by using physiologic classification. Last, in the future, the assumption that myoclonus arises from a single area of the nervous system will likely be challenged. Local area networks and even distributed networks may be operant in the genesis of myoclonus.

CONCLUSION

The many types and etiologies of myoclonus may at first seem confusing. An efficient and pragmatic evaluation of myoclonus that uses the clinical presentation classification scheme offers the best approach to define the etiology. Further evaluation that results in physiologic classification can lead to further understanding of the myoclonus. Combining the information from the etiology with the determined or presumed physiology is used to develop the best treatment strategy. Treatment is often unsatisfactory, and more research into treatment and controlled clinical studies are desperately needed. Rather than presuming that myoclonus arises from a single area, it may be that a network abnormality produces myoclonus in some syndromes. Further research on myoclonus generation mechanisms should shed light on future treatment possibilities.

REFERENCES

1 Marsden CD, Hallett M, Fahn S. The nosology and pathophysiology of myoclonus. In: Marsden CD, Fahn S, editors. Movement disorders. London, United Kingdom: Butterworths, 1982:196–248.

2 van der Salm SM, de Haan RJ, Cath DC, et al. The eye of the beholder: inter-rater agreement among experts on psychogenic jerky movement disorders. J Neurol Neurosurg Psychiatry 2013; 84(7):742–747. doi:10.1136/jnnp-2012-304113.

3 Caviness JN, Alving LI, Maraganore DM, et al. The incidence and prevalence of myoclonus in Olmsted County, Minnesota. Mayo Clin Proc 1999;74(6):565–569. doi:10.4065/74.6.565.

4 Caviness JN. Treatment of myoclonus. Neurotherapeutics 2014;11(1):188–200. doi: 10.1007/s13311-013-0216-3.

5 Caviness JN. Clinical neurophysiology of myoclonus. In: Hallett M, editor. Movement disorders. Handbook of clinical neurophysiology. Vol 1. Amsterdam, the Netherlands: Elsevier, 2003: 521–548.

6 Avanzini G, Shibasaki H, Rubboli G, et al. Neurophysiology of myoclonus and progressive myoclonus epilepsies. Epileptic Disord 2016; 18(S2):11–27. doi:10.1684/epd.2016.0835.

7 Caviness JN. Epileptic myoclonus. In: Sirven JI, Stern JM, editors. Atlas of video-EEG monitoring. New York, NY: McGraw-Hill Medical, 2011: 309–328.

8 Genton P, Thomas P, Kasteleijn-Noist Trenité DG, et al. Clinical aspects of juvenile myoclonic epilepsy. Epilepsy Behav 2013;28(suppl 1):S8–S14. doi:10.1016/j.yebeh.2012.10.034.

9 Brown P, Thompson PD, Rothwell JC, et al. Axial myoclonus of propriospinal origin. Brain 1991; 114(pt 1A):197–214. doi:10.1093/oxfordjournals.brain.a101857.

10 Roze E, Apartis E, Clot F, et al. Myoclonus-dystonia: clinical and electrophysiologic pattern related to SGCE mutations. Neurology 2008; 70(13):1010–1016. doi:10.1212/01.wnl.0000297516.98574.c0.

11 Caviness JN. Segmental Myoclonus. In: Albanese A, Jankovic J, editors. Hyperkinetic movement disorders. West Sussex, United Kingdom: Wiley-Blackwell, 2012:221–236.

12 Deuschl G, Mischke G, Schenck E, et al. Symptomatic and essential rhythmic palatal myoclonus. Brain 1990;113(pt 6):1645–1672. doi:10.1093/brain/113.6.1645.

13 Bono F, Salvino D, Sturniolo M, et al. Botulinum toxin is effective in myoclonus secondary to peripheral nerve injury. Eur J Neurol 2012;19: e92–e93. doi:10.1111/j.1468-1331.2012.03780.x.

14 Rose Russell AL, Knight W, Oware A, Fuller GN. A unique case of peripheral myoclonus. J Neurol Neurosurg Psychiatry 2012;84(1):117–118. doi: 10.1136/jnnp-2012-303795.

15 Shin HW, Ye BS, Kim J, et al. The contribution of a spinal mechanism in developing peripheral myoclonus: a case report. Mov Disord 2007; 22(9):1350–1351. doi:10.1002/mds.21418.

16 Frauscher B, Gabella D, Mitterling T, et al. Motor events during healthy sleep: a quantitative polysomnographic study. Sleep 2014;37(4): 763–773. doi:10.5665/sleep.3586.

17 Chokroverty S, Manocha MK, Duvoisin RC. A physiologic and pharmacologic study in anticholinergic-responsive essential myoclonus. Neurology 1987;37(4):608–615. doi:10.1212/WNL.37.4.608.

18 Asmus F, Salih F, Hjermind LE et al. Myoclonus-dystonia due to genomic deletions in the epsilon-sarcoglycan gene. Ann Neurol 2005; 58(5):792–797. doi:10.1002/ana.20661.

19 Marras C, Lang A, van de Warrenburg BP, et al. Nomenclature of genetic movement disorders: recommendations of the international Parkinson and movement disorder society task force. Mov Disord 2016;31(4):436–457. doi:10.1002/mds.26527.

20 Tan KM, Lennon VA, Klein CJ, et al. Clinical spectrum of voltage-gated potassium channel autoimmunity. Neurology 2008;70(20):1883–1890. doi:10.1212/01.wnl.0000312275.04260.a0.

21 Geschwind MD, Tan KM, Lennon VA, et al. Voltage-gated potassium channel autoimmunity mimicking Creutzfeldt-Jakob disease. Arch Neurol 2008;65(10):1341–1346. doi:10.1001/archneur.65.10.1341.

22 Michelucci R, Pasini E, Riguzzi P, et al. Myoclonus and seizures in progressive myoclonus epilepsies: pharmacology and therapeutic trials. Epileptic Disord 2016;18(2):145–153. doi:10.1684/epd.2016.0861.

23 Marsden CD, Harding QE, Obeso JA, Lu CS. Progressive myoclonic ataxia (the Ramsay Hunt syndrome). Arch Neurol 1990;47(10):1121–1125. doi:10.1001/archneur.1990.00530100091019.

24 Charlesworth G, Balint B, Mencacci NE, et al. SLC25A46 mutations underlie progressive myoclonic ataxia with optic atrophy and neuropathy. Mov Disord 2016;31(8):1249–1251. doi:10.1002/mds.26716.

25 Caviness JN, Adler CH, Beach T, et al. Myoclonus in Lewy body disorders. In: Fahn S, Frucht SJ, Hallett M, Truong D, editors. Myoclonus and paroxysmal dyskinesias. Advances in neurology. Volume 89. New York, NY: Lippincott Williams & Wilkins, 2002:23–30.

26 Sifoglu A, Gunduz A, Kiziltan G. Dopaminergic medication unrelated myoclonus is less related to tremor in idiopathic Parkinson's disease. Neurol Sci 2017;38(4):679–682.

27 Beagle AJ, Darwish SM, Ranasinghe KG, et al. Relative incidence of seizures and myoclonus in Alzheimer's disease, dementia with Lewy bodies, and frontotemporal dementia. J Alzheimers Dis 2017;60(1):211–223.

28 Okuma Y, Fujishima K, Miwa H, et al. Myoclonic tremulous movements in multiple system atrophy are a form of cortical myoclonus. Mov Disord 2005;20(4);451–456. doi:10.1002/mds.20346.

29 Grijalvo-Perez AM, Litvan I. Corticobasal degeneration. Semin Neurol 2014;34(2):160–173. doi:10.1055/s-0034-1381734.

30 Iwasaki Y. Creutzfeldt-Jakob disease. Neuropathology 2017;37(2):174–188.

31 Alvarez M, Caviness JN. Primary progressive myoclonus of aging. Mov Disord 2008;23(12): 1658–1664. doi:10.1002/mds.22085.

32 Sweeney M, Sweeney Matthew, Soldan MMP, Clardy SL. Antineuronal nuclear autoantibody type 1/Anti-Hu-associated opsoclonus myoclonus and epilepsia partialis continua: case report and literature review. Pediatr Neurol 2016;65:86–89. doi:10.1016/j.pediatrneurol.2016.08.024.

33 Honorat JA, McKeon A. Autoimmune movement disorders: a clinical and laboratory approach. Curr Neurol Neurosci Rep 2017;17(1):4. doi:10.1007/s11910-017-0709-2.

34 Caviness JN, Brown P. Myoclonus: current concepts and recent advances. Lancet Neurol 2004;3(10):598–607. doi:10.1016/S1474-4422(04)00880-4.

35 Gupta HV, Caviness JN. Post-hypoxic myoclonus: current concepts, neurophysiology, and treatment. Tremor Other Hyperkinet Mov (N Y) 2016;6:409. doi:10.7916/D89C6XM4.

36 Ong MT, Sarrigiannis PG, Baxter PS. Post-anoxic reticular reflex myoclonus in a child and proposed classification of post-anoxic myoclonus. Pediatr Neurol 2017;68:68–72. doi:10.1016/j.pediatrneurol.2016.12.014.

37 Deuschl G, Wilms H. Palatal tremor: the clinical spectrum and physiology of a rhythmic movement disorder. In: Fahn S, Frucht SJ, Hallett M, Truong D, editors. Myoclonus and paroxysmal dyskinesias. Advances in neurology. Volume 89. New York, NY: Lippincott Williams & Wilkins, 2002:115–130.

38 Slengerik-Hansen J, Ovesen T. Botulinum toxin treatment of objective tinnitus because of essential palatal tremor: a systematic review. Otol Neurotol 2016;37(7):820–828. doi:10.1097/MAO.0000000000001090.

39 Antelmi E, Provini F. Propriospinal myoclonus: the spectrum of clinical and neuro physiological phenotypes. Sleep Med Reviews 2015;22:54–63. doi:10.1016/j.smrv.2014.10.007.

40 Hassan A, van Gerpen JA. Orthostatic tremor and orthostatic myoclonus: weight-bearing hyperkinetic disorders: a systematic review, new insights, and unresolved questions. Tremor Other Hyperkinet Mov (N Y) 2016;6:417. doi:10.7916/D84X584K.

41 Ikeda A, Kakigi R, Funai N, et al. Cortical tremor: a variant of cortical reflex myoclonus. Neurology 1990;40(10):1561–1565. doi:10.1212/WNL.40.10.1561.

42 Coppola A, Santulli L, Del Gaudio L, et al. Natural history and long-term evolution in families with autosomal dominant cortical tremor, myoclonus, and epilepsy. Epilepsia 2011;52(7):1245–1250. doi:10.1111/j.1528-1167.2011.03017.x.

43 Wilkins DE, Hallett M, Erba G. Primary generalized epileptic myoclonus: a frequent manifestation of minipolymyoclonus of central origin. J Neurol Neurosurg Psychiatry 1985;48(6):506–516.

44 Genton P, Gélisse P. Antimyoclonic effect of levetiracetam. Epileptic Disord 2000;2(4): 209–212.

45 Striano P, Manganelli F, Boccella P, et al. Levetiracetam in patients with cortical myoclonus: a clinical and electrophysiological study. Mov Disord 2005;20(12):1610–1614. doi:10.1002/mds.20530.

46 Frucht SJ, Louis ED, Chuang C, Fahn S. A pilot tolerability and efficacy study of levetiracetam in patients with chronic myoclonus. Neurology 2001;57(6):1112–1114. doi:10.1212/WNL.57.6.1112.

47 Magaudda A, Gelisse P, Genton P. Antimyoclonic effect of levetiracetam in 13 patients with Unverricht-Lundborg disease: clinical observations. Epilepsia 2004;45(6):678–681. doi:10.1111/j.0013-9580.2004.56902.x.

48 Goldberb MA, Dorman JD. Intention myoclonus: successful treatment with clonazepam. Neurology 1976;26(1):24–26. doi:10.1212/WNL.26.1.24.

49 Fahn S. Posthypoxic action myoclonus: review of the literature and report of two new cases with response to valproate and estrogen. Adv Neurol 1979;26:49–84.

50 Obeso JA, Artieda J, Rothwell JC, et al. The treatment of severe action myoclonus. Brain 1989;112(pt 4):765–777. doi:10.1093/brain/112.3.765.

51 Arpesella R, Dallocchio C, Arbasino C. A patient with intractable posthypoxic myoclonus (Lance–Adams syndrome) treated with sodium oxybate. Anaesth Intensive Care 2009;37: 314–318.

52 Kälviäinen R, Genton P, Andermann E, et al. Brivaracetam in Unverricht-Lundborg disease (EPM1): results from two randomized, double-blind, placebo-controlled studies. Epilepsia 2016;57(2):210–221. doi:10.1111/epi.13275.

53 Crespel A, Gelisse P, Tang NP, Genton P. Perampanel in 12 patients with Unverricht-Lundborg disease. Epilepsia 2017;58(4):543–547. doi:10.1111/epi.13662.

54 Ramdhani RA, Frucht SJ, Kopell BH. Improvement of post-hypoxic myoclonus with bilateral pallidal deep brain stimulation: a case report and review of the literature. Tremor Other Hyperkinet Mov (N Y) 2017;7:461. doi:10.7916/D8NZ8DXP.

55 Nevitt SJ, Sudell M, Weston J, et al. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. Cochrane Database of Systematic Reviews 2017;(12):CD011412. doi:10.1002/14651858.CD011412.pub3.

56 Buchanan N. The use of lamotrigine in juvenile myoclonic epilepsy. Seizure 1996;5:149–151. doi:10.1016/S1059-1311(96)80110-5.

57 Steinig I, von Podewils F, Möddel G, et al. Postmarketing experience with brivaracetam in the treatment of epilepsies: a multicenter cohort study from Germany. Epilepsia 2017;58(7): 1208–1216. doi:10.1111/epi.13768.

58 Caviness JN, Forsyth PA, Layton DD, McPhee TJ. The movement disorder of adult opsoclonus. Mov Disord 1995;10(1):22–27. doi:10.1002/mds.870100106.

59 Rocha H, Linhares P, Chamadoira C, et al. Early deep brain stimulation in patients with myoclonus-dystonia syndrome. J Clin Neurosci 2016;27:17–21. doi:10.1016/j.jocn.2015.08.034.

60 Rath JJ, Tavy DL, Snoeck-Streef I, Contarino MF. Sustained remission of segmental myoclonus due to peripheral nerve injury after treatment with onabolinumtoxinA. Parkinsonism Relat Disord 2015;21(9):1111–1112. doi:10.1016/j.parkreldis.2015.07.001.

61 Chaudhry N, Srivastava A, Joshi L. Hemifacial spasm: the past, present and future. J Neurol Sci 2015;356(1–2):27–31. doi:10.1016/j.jns.2015.06.032.