**Myoclonus: Definition**

Quick muscle jerks  
Either irregular or rhythmic,  
but always simple
Myoclonus

- Spontaneous
- Action myoclonus: activated or accentuated by voluntary movement
- Reflex myoclonus: activated or accentuated by sensory stimulation

Myoclonus

- Focal: involving only few adjacent muscles
- Generalized: involving most or many of the muscles of the body
- Multifocal: involving many muscles, but in different jerks
Differential diagnosis of myoclonus

- Simple tics
- Some components of chorea
- Tremor
- Peripheral disorders
  - Fasciculation
  - Myokymia
  - Hemifacial spasm

Classification of Myoclonus

Site of Origin

- Cortex
  - Cortical myoclonus, epilepsy partialis continua, cortical tremor
- Brainstem
  - Reticular myoclonus, exaggerated startle, palatal myoclonus
- Spinal cord
  - Segmental, propriospinal
- Peripheral
  - Rare, likely due to secondary CNS changes
Classification of myoclonus to guide therapy

- First consideration: Etiological classification
  - *Is there a metabolic encephalopathy to be treated? Is there a tumor to be removed? Is a drug responsible?*

- Second consideration: Physiological classification
  - *Can the myoclonus be treated symptomatically even if the underlying condition remains unchanged?*

Myoclonus: Physiological Classification

- Epileptic
- Non-epileptic

The basic question to ask is whether the myoclonus is a “fragment of epilepsy” or not.
Differentiation of epileptic and non-epileptic myoclonus: Electrophysiological criteria

- EMG burst length
- EMG antagonist muscle relationship
- EEG correlate

Two physiological types of myoclonus

A

B

BICEPS

TRICEPS

F. FLEX.

F. EXT.

100 MS
Differentiation of epileptic and non-epileptic myoclonus: 
Electrophysiological criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Epileptic myoclonus</th>
<th>Non-epileptic myoclonus</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMG burst length</td>
<td>25 to 75 ms</td>
<td>50 to 300 ms</td>
</tr>
<tr>
<td>EMG antagonist muscle relationship</td>
<td>Always synchronous</td>
<td>Synchronous or alternating</td>
</tr>
<tr>
<td>EEG correlate</td>
<td>Typically present</td>
<td>Always absent</td>
</tr>
</tbody>
</table>

Types of Epileptic Myoclonus

- Cortical Reflex Myoclonus
- Reticular Reflex Myoclonus
- Primary Generalized Epileptic Myoclonus
C-Reflex to Cutaneous Stimulation

Cortical reflex myoclonus: Reflex jerk and SEP
Cortical reflex myoclonus: spontaneous jerk

Asterixis or Negative Myoclonus
Anticonvulsants used for myoclonus

<table>
<thead>
<tr>
<th>AGENT</th>
<th>DOSE (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam</td>
<td>3 to 20</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>1000 to 2000</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1000 to 3000</td>
</tr>
<tr>
<td>Primidone</td>
<td>500 to 750</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>60 to 180</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>100 to 600</td>
</tr>
<tr>
<td>Brivaracetam (?)</td>
<td>150 (?)</td>
</tr>
<tr>
<td>Perampanel</td>
<td>2 to 4</td>
</tr>
</tbody>
</table>

Avoid Phenytoin, Gabapentin and Carbamazepine

2 or 3 drugs in combination might be better than a single drug
Negative Myoclonus

- Treatment can be very difficult!
- Two patients have responded to levetiracetam (Gelisse 2003; Yu et al. 2009)
- Some success has been seen with the myoclonus in childhood partial epilepsy using ethosuximide (Capovilla et al. 1999)
  - And likely other anticonvulsants, although not reported
- One patient with post-hypoxic positive and negative was improved with bilateral GPi DBS
  - Ramdhani et al. 2017 TOHM May 19;7:461
- Perampanel – see next slide
Single case report with bouncy gait as primary symptom
  Negative myoclonus not demonstrated as etiologic
  No negative myoclonus in upper extremities (by exam)

Non-epileptic Myoclonus

- Dystonic myoclonus and fragments of other involuntary movement disorder
- Exaggerated startle
- Physiologic phenomena (e.g., hypnic jerk)
- Periodic movements in sleep (PMS)
- Segmental myoclonus
- Functional myoclonus
Dystonic Myoclonus

Myoclonus: Etiological Classification

• Physiologic: normal phenomena
• Epileptic: a manifestation in patients with epilepsy as their major problem
• Symptomatic
Types of Symptomatic Myoclonus

- Genetic disorders
  - Including the Progressive Myoclonus Epilepsies
- Basal ganglia disorders
- Dementias
- Viral encephalopathies
- Metabolic encephalopathies; endocrine disorders
- Autoimmune
- Toxic encephalopathies; including drugs
- Physical encephalopathies: including hypoxia
- Focal CNS damage
- Functional

Progressive Myoclonus Epilepsies

Kälviäinen R. Semin Neurol 2015; 35: 293

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Gene tests</th>
<th>Enzymes analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Unverricht-Lundbreg disease (PM1)</td>
<td>Gene test: EPMT1 (CSTB) mutation analysis</td>
<td>Leukocyte enzyme analysis: PPT1, TFP1, CTSO</td>
</tr>
<tr>
<td>2. Lafora body disease (PM2)</td>
<td>Skin biopsy: Lafora bodies</td>
<td>Leukocyte enzyme analysis: CLN1, CLN2, CLN3, CLN11 (CTR1) mutation analysis</td>
</tr>
<tr>
<td>3. Neuronal ceroid lipofuscinoses (NCL)</td>
<td>Gene tests: EPMT1A or EPMT2B (ATMRC1) mutation analysis</td>
<td>Leukocyte enzyme analysis: CLN5, CLN6, CLN7 (MFSO), CLN8, CLN10 (CTSO), CLN11 (GRN), CLN12 (MP1, 2), CLN13 (CTSO), CLN14 (KCTD7) mutation analysis</td>
</tr>
<tr>
<td>4. Sialidosis</td>
<td>Urine: Sialo-oligosaccharides</td>
<td>Leukocyte enzyme analysis: Neuraminidase</td>
</tr>
<tr>
<td>5. Myoclonus epilepsy and ragged-red fibers (MERF)</td>
<td>Plasma lactate and pyruvate</td>
<td>Leukocyte enzyme analysis: Neuraminidase</td>
</tr>
<tr>
<td>6. Type 3 neuropathic Gaucher disease</td>
<td>Muscle biopsy: Ragged-red fibers</td>
<td>Leukocyte enzyme analysis: (β-glucocerebrosidase)</td>
</tr>
<tr>
<td>7. Dentatorubral-pallidoluysian atrophy</td>
<td>Gene test: GBA mutation analysis</td>
<td>Leukocyte enzyme analysis: (β-glucocerebrosidase)</td>
</tr>
<tr>
<td>8. Action myoclonus-renal failure syndrome (AMRF; EPAM)</td>
<td>Gene test: SCARB2/UMPF2 mutation analysis</td>
<td>Leukocyte enzyme analysis: (β-glucocerebrosidase)</td>
</tr>
<tr>
<td>9. PME-ataxia syndrome (EPAM5)</td>
<td>Gene test: PROKLE mutation analysis</td>
<td>Leukocyte enzyme analysis: (β-glucocerebrosidase)</td>
</tr>
<tr>
<td>10. North Sea PME (EPAM6)</td>
<td>Gene test: GOSR2 mutation analysis</td>
<td>Leukocyte enzyme analysis: (β-glucocerebrosidase)</td>
</tr>
</tbody>
</table>

Also: KCNC1, BSCL2, KCNA2, and likely more...
Progressive Myoclonic Epilepsy: EPM1

• Unverricht-Lundborg
  – Also known as: Ramsay-Hunt syndrome, Baltic myoclonus epilepsy

• Autosomal recessive condition
  – mutation in the gene encoding cystatin B, a cysteine protease inhibitor

EPM1: Treatment

• Avoid phenytoin!
  – ...and lamotrigine

• Use valproate with possible supplementation with clonazepam, levetiracetam, topiramate and zonisamide

• Consider perampanel
  – Inhibits postsynaptic AMPA receptors
    – Crespel et al. 2017 Epilepsia 58: 543
    – Iijima et al. 2019 eNeurologicalSci 17:100215
    – Canafoglia et al. 2019 Epilepsy Res 156:106191
  • For all types of EPM
Myoclonus: mitochondrial disorders

- MERRF, myoclonus epilepsy and ragged red fiber syndrome can be due to mutation in G8363A in the mitochondrial DNA tRNA (Lys) gene
- Ekbom’s syndrome of photomyoclonus, cerebellar ataxia and cervical lipoma is associated with the tRNA(Lys) A8344G mutation in mitochondrial DNA
- Mutant NDUFV1 subunit of mitochondrial complex I causes leukodystrophy and myoclonic epilepsy

DBS for Progressive Myoclonic Epilepsy

- Targets have included STN, SNr
- Can benefit positive and negative myoclonus
**Viral encephalopathies**

- Herpes simplex encephalitis
- Subacute sclerosing panencephalitis (SSPE)
  - Therapy
    - Immunomodulatory therapy with interferon and isoprinosine has had some success
    - Carbamazepine can be useful symptomatically (Yigit & Sarikaya, 2006; Rivikumar & Crawford, 2013)

- AIDS-dementia complex
- Chikungunya meningoencephalitis
- Nipah virus
- SARS-CoV-2

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**Generalized myoclonus in COVID-19**

3 patients with generalized positive and negative myoclonus
All in the “inflammatory phase” of the disease
All improved to some extent with immunotherapy
Metabolic encephalopathies; endocrine disorders

- Hepatic failure
- Renal failure
- Hyponatremia
- Hypoglycemia
- Non-ketotic hyperglycinemia
- Hyperthyroidism
- Biotin (vitamin H) deficiency

Note: These are generally treatable!

Autoimmune disorders

- Opsoclonus-myoclonus syndrome
- Progressive encephalomyelitis with rigidity and myoclonus (PERM)
- Celiac disease
  - Stimulus sensitive foot myoclonus
    - Jesus et al. 2019 Mov Disord Clin Pract
  - (discussed with the ataxias)
Opsoclonus-myoclonus syndrome

- Settings include infections, toxins and a paraneoplastic syndrome. In childhood the syndrome is often associated with neuroblastoma.
- Associated with a distinctive pattern of serum IgM and IgG binding to neural tissues and antigens

### Table 1: Causes of opsoclonus–myoclonus syndrome.

<table>
<thead>
<tr>
<th>Causes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>[9]</td>
</tr>
<tr>
<td>Mumps</td>
<td>[10]</td>
</tr>
<tr>
<td>Coronavirus B3</td>
<td>[11]</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>[12]</td>
</tr>
<tr>
<td>Epstein–Barr virus</td>
<td>[14]</td>
</tr>
<tr>
<td>West Nile virus</td>
<td>[15]</td>
</tr>
<tr>
<td>Streptococci</td>
<td>[16]</td>
</tr>
<tr>
<td>Mycoplasma pneumonia</td>
<td>[17]</td>
</tr>
<tr>
<td>Dengue virus</td>
<td>[18]</td>
</tr>
<tr>
<td>Human herpes virus type 6</td>
<td>[19]</td>
</tr>
<tr>
<td>HHV</td>
<td>[19]</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>[19]</td>
</tr>
<tr>
<td>Paraneoplastic</td>
<td></td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>[20]</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>[21]</td>
</tr>
<tr>
<td>SCLC (adults)</td>
<td>[22]</td>
</tr>
<tr>
<td>Breast cancer (adults)</td>
<td></td>
</tr>
<tr>
<td>Ovarian teratoma, neuroepithelial</td>
<td>[23]</td>
</tr>
<tr>
<td>Carcinoma, non-SCLC (adults, esophagus)</td>
<td>[23–24]</td>
</tr>
<tr>
<td>Carcinoma</td>
<td></td>
</tr>
<tr>
<td>Toxic</td>
<td></td>
</tr>
<tr>
<td>Thallium</td>
<td>[25]</td>
</tr>
<tr>
<td>Strychnine</td>
<td>[26]</td>
</tr>
<tr>
<td>Cocaine</td>
<td>[27]</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td>Amantadine</td>
<td>[28]</td>
</tr>
<tr>
<td>Lithium</td>
<td>[29]</td>
</tr>
<tr>
<td>Phenytoine</td>
<td>[30]</td>
</tr>
<tr>
<td>SCLC small-cell lung cancer</td>
<td>[31,32]</td>
</tr>
</tbody>
</table>

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53
Adult-Onset Opsoclonus-Myoclonus Syndrome

James P. Klaus, MD; J. Eric Ahlskog, PhD, MD; Sean J. Pitcock, MD; Joseph Y. Matsuzono, MD; Allen J. Aksun, MD; J. D. Bartleson, MD; Rajeev Kumar, MD; Kathleen F. McEvoy, MD, PhD; Andrew McKeon, MD


- 21 new adult cases and review of 116 literature patients
- Causes:
  - Paraneoplastic (most common antibody, antineuronal nuclear antibody type 2, anti-Ri)
  - Idiopathic
  - Parainfectious (often HIV)
  - Toxic/metabolic
  - Autoimmune (anti-NMDA antibody)

Opsoclonus-myoclonus syndrome: Treatment

- Treat the underlying cause if possible
  - For example, remove the underlying tumor
- Treat the autoimmune aspect for symptomatic treatment with ACTH, steroids or plasmapheresis
- Autologous stem cell transplantation (Johnston et al. 2018)
Table 3 Overview of medications and toxic agents associated with myoclonus

<table>
<thead>
<tr>
<th>Drug/toxic agent group</th>
<th>Specific substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td>Lithium</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Bismuth, Methyl Bromide</td>
</tr>
</tbody>
</table>

**Table 3** Overview of medications and toxic agents associated with myoclonus

Anticonvulsants: Phenobarbital, carbamazepine, sodium valproate, gabapentin, pregabalin, levetiracetam, phenyltoin, tiagabine, valproic acid, lamotrigine, benzodiazepines, and lamotrigine.

Lithium: Lithium, carbamazepine, valproic acid, and lamotrigine.

Bismuth: Methyl Bromide.

Myoclonus: basal ganglia disorders

- Parkinson disease
  - Unsteadiness when standing might be due to orthostatic myoclonus
- Dopa-dyskinesias
- Multiple system atrophy
- Huntington disease
- Corticobasal degeneration
  - Note short latency reflex myoclonus
- PSP
- Dystonia
Dystonic Myoclonus

- Any type of dystonia, including DYT1
  - Treat as the dystonia, e.g., trihexyphenidyl, botulinum toxin, DBS
    - DBS of GPi or STN
- Myoclonus dystonia DYT11 (SGCE)
  - Alcohol (ethanol) responsive
  - Trihexyphenidyl, clonazepam, tetrabenazine, zonisamide
  - DBS of GPi or thalamus
- Mutations also in KCTD17, CACNA1B, RELN, ANO3, SCN8A, ADCY5, TITF1, TUBB2B, KCNN2 (some questionable)

Dementias

- Alzheimer disease
- Creutzfeld-Jakob disease
- FTLD-TDP (frontotemporal lobar degeneration with TDP-43 positive inclusions)
Focal CNS damage

- Tumors
- Angiomas
- Encephalitis

- Note that treatment sometimes can be directed surgery to the offending lesion

Physical encephalopathies

- Post-hypoxic myoclonus (Lance-Adams syndrome)
- Trauma
- Heat stroke
- Electric shock
- Decompression injury
78 patients: 11 (14.1%) recovered at discharge
Predictive features:
  - pupillary and corneal reflexes
  - flexion or better motor response
  - EEG continuity and reactivity and no burst suppression
  - no anoxic injury on MRI

Chronic Posthypoxic Myoclonus
Lance and Adams 1963

• Action myoclonus
• Postural lapses (negative myoclonus)
• Association with cerebellar ataxia, gait disturbance and grand mal seizures
Chronic Posthypoxic Myoclonus

- Werhahn et al. 1997 reported 14 cases
- Mean duration of coma 9 days (range, 4 to 28)
- Myoclonus first appeared within a few days in 9 patients, 2 weeks in 2, and 3 months in 1
- All had multifocal action myoclonus, and 11 had stimulus-sensitive myoclonus

Chronic Posthypoxic Myoclonus

Werhahn et al. 1997

- Epilepsy was not a major feature, only 2 had continuing seizures
- Cognitive deficits were found in seven patients and were usually mild
- There was late improvement in the myoclonus and the level of disability in all but one patient
Exaggerated Startle Syndromes

- Startle can be increased by virtue of
  - Increased magnitude
  - Lack of habituation
Exaggerated Startle Syndromes

- Hyperekplexia
  - Hereditary
  - Symptomatic
    - brain stem lesions, perinatal hypoxic-ischemic encephalopathy, thalamic lesions, schizophrenia, post-traumatic stress syndrome, Tourette syndrome, drugs (amphetamine, cocaine), idiopathic
- Startle epilepsy
- Latah syndrome

Hereditary Hyperekplexia

- Genetic disorder due to several possible abnormalities of glycine transmission
- Commonly autosomal dominant, but can be recessive or X-linked
- The alpha-1 subunit of the glycine receptor is most commonly affected, but it can also be the beta subunit, or very rarely in related proteins gephyrin and collybistin
- Also the presynaptic glycine transporter 2 (GlyT2, specifically SLC6A5) can be affected
Hereditary Hyperekplexia

- Characterized by excessive startle, then stiffening that can cause falls
- Babies are very stiff (stiff baby syndrome) and can have sudden infant death syndrome (SIDS)
- Treatment
  - Clonazepam is treatment of choice
    - 0.03 to 0.2 mg/kg/day

Exaggerated Startle Syndromes

- Hyperekplexia
  - Hereditary
  - Symptomatic
    - brain stem lesions, perinatal hypoxic-ischemic encephalopathy, thalamic lesions, schizophrenia, post-traumatic stress syndrome, Tourette syndrome, drugs (amphetamine, cocaine), idiopathic
- Startle epilepsy
- Latah syndrome
Latah Syndrome

- Consists of a startle, secondary behavior such as striking out, and an emotional response
- Patients also have echolalia and echopraxia
- Similar syndromes in different cultures, for example, the same as Jumping Frenchmen of Maine

Latah syndrome

- Latah (Malaysia)
- Jumping (Jumping Frenchmen of Maine)
- Myriachit (Siberia)
- Yaun (Burma)
- Bah-tsche (Thailand)
- Mali-mali (Philippines)
- Lapp panic (Lapland)
- Imu (Japan)
- Goosey (Southern United States)
- Ragin’Cajuns (Louisiana)
Auditory Startle

Both responses are enhanced, but the late response is clinically more significant.

Spinal myoclonus

- **Rhythmic**
  - spontaneous, persistent rhythmic repetitive movements usually unaffected by sleep

- **Propriospinal**
  - symmetric flexion of neck, trunk, hips and knees
  - jerks can be spontaneous or stimulus induced
Spinal myoclonus

- Etiologies
  - Trauma, tumor, infection, disk herniation

Spinal Myoclonus

[Diagram showing EMG traces labeled for different muscles (Quadiceps, Hamstrings, Tibialis Ant, Gastrocnemius) on the right and left sides.]

Davis et al. 1981
Spinal Myoclonus from a Spinal Cord Tumor

A, Sagittal T1 non-contrast image demonstrating mass at the level of C7 consistent with primary intramedullary cord tumor (arrow). B, Axial T2 demonstrating intramedullary mass at C7, left of the midline (arrow).

Nicholas M. Allen, Margaret M. Moran, Mary D. King
Not all Twitching is Epileptic! Hand Myoclonus in a Boy with Spinal Cord Tumor
The Journal of Pediatrics Volume 162, Issue 2 2013 431 - 431.e1
http://dx.doi.org/10.1016/j.jpeds.2012.07.062

Propriospinal Myoclonus

- Controversial entity
- Non-rhythmic axial jerks that lead to symmetrical flexion of neck, trunk, hips and knees
- Jerks can be spontaneous or stimulus induced
- Myoclonus starts in mid-thoracic region and propagates at about 5 m/s both rostrally and caudally
Propriospinal Myoclonus

- Esposito et al. *Movement Disorders* 2014 have reviewed the literature on apparent symptomatic cases as well as their own cases, and concluded that even these seem mostly functional
  - Brown (editorial) notes that this may be true, but still there might be rare true cases
- Van der Salm et al. *Neurology* 2014 have also done literature review and identified 58% as functional
Palatal tremor/myoclonus
A type of segmental myoclonus

• There are two separate disorders!
  – Essential palatal tremor (EPT) which manifests as an ear click
  – Symptomatic palatal tremor (SPT) which is associated with cerebellar disturbances

• Essential palatal tremor
  – Ear click
  – Tensor veli palatini muscle
  – Stops during sleep
  – Hypertrophy of inferior olive is NOT found

• Symptomatic palatal tremor
  – Levator veli palatini muscle
  – May be accompanied by synchronous activity of adjacent muscles
  – Continues during sleep
  – Exerts remote effect on limb muscles
  – Associated with ipsilateral cerebellar dysfunction
  – Contralateral hypertrophy of inferior olive
MRI Scan showing hypertrophy of the inferior olives.
Treatment of Palatal Tremor

- The ear click of Essential Palatal Tremor is the symptom that requires treatment.

- Drugs
  - clonazepam, tryptophan, carbamazepine, trihexyphenidyl, ceruletid, sumatriptan

- Focal injection of botulinum toxin

Note: Some of these patients are functional!

Functional (Psychogenic) myoclonus

- Clinical features incongruous with “organic myoclonus”
- Evidence for underlying psychopathology
- Improvement with distraction or placebo
- Presence of false weakness or incongruous sensory loss

— Monday and Jankovic 1993
Figure 1 A novel eight-step diagnostic algorithm for myoclonus

- History and physical exam
- Clinical neurophysiology
- Imaging
- Lab tests
- (Genetic studies)

Medication or toxic agents


Electrophysiologic testing aids diagnosis and subtyping of myoclonus

Figure 1 Overview of the stages of clinical assessment and diagnosis undertaken in this study

- Step 1: Initial clinical diagnosis
- Step 2: Electrophysiologic testing vs initial diagnosis
- Step 3: Expert opinion after electrophysiologic testing – final diagnosis

CM = cortical myoclonus; F = functional jerks; MD = movement disorder; MMS = multiple myoclonus subtypes; SCM = subcortical myoclonus; SM = spinal myoclonus.
Final Message

• There are many types of myoclonus.
• Diagnosis can be made clinically and aided by clinical neurophysiology
• Treatments need to be suited to the diagnosis.