Myoclonus in the critically ill: Diagnosis, management and clinical impact

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Abstract

Myoclonus is the second most common involuntary non-epileptic movement in intensive care units following tremor-like gestures. Although there are several types of myoclonus, they remain underappreciated and their diagnostic and prognostic associations are largely ignored.

This review discusses clinical, electrophysiological, neuroanatomical, and neuroimaging characteristics of different types of myoclonus in critically ill adults along with their prognostic impact and treatment options.

Myoclonus is characterized by a sudden, brief, and sometimes repetitive muscle contraction of body parts, or a brief and sudden cessation of tonic muscle innervation followed by a rapid recovery of tonus. Myoclonus can resemble physiologic and other pathologic involuntary movements. Neurologic injuries, anesthetics, and muscle relaxants interfere with the typical appearance of myoclonus. Identifying “real myoclonus” and determining the neuroanatomical origin is important, as treatment responses depend on the involved neuroanatomical structures. The identification of the type of myoclonus, the involved neuroanatomical structures and the associated illnesses is essential to direct treatment.

In conclusion, the combined clinical, electrophysiological and neuroradiological examination reliably uncovers the neuroanatomical sources and pathophysiology of myoclonus. Recognizing cortical myoclonus is critical, as it is treatable and may progress to generalized convulsive seizures or status epilepticus.

Keywords: Myoclonus; diagnosis; treatment; prognosis; critical illness; neurocritical care.

1. Introduction

Myoclonus is the second most common involuntary non-epileptic movement in intensive care units (ICUs) following tremor-like motions (Benbadis et al.,2010).

However, myoclonic jerks are not pathognomonic of any particular disease.

Despite the growing body of evidence that myoclonus accompanies a number of critical illnesses, it remains underappreciated and its diagnostic and prognostic impact is largely ignored.

The aim of this review is to provide a comprehensive overview of the clinical, electrophysiological, neuroanatomical, and neuroimaging characteristics of the different types of myoclonus in critically ill adult patients along with the prognostic impact in critical care and current treatment options.

2. Definition, phenomenology and clinical classification of myoclonus

Myoclonus is a sudden, brief, abrupt twitching of body parts involving the face, extremities, and trunk(Fahn et al.,1986) caused by an abnormally increased excitability of neurons leading to muscle contractions (i.e., positive myoclonus), or a sudden brief loss of muscle tonus followed by a rapid recovery of tonus (i.e., negative myoclonus) that may appear in clusters called “flapping tremor” or “asterixis”(Artieda et al.,1992; Butz et al.,2014; Shibasaki,1995; Young and Shahani,1986) and can be associated with epileptic events(Baumgartner et al.,1996; Belcastro et al.,2011; Meletti et al.,2000; Rubboli et al.,1995; Song et al.,2006; Tassinari et al.,1995) (Figure 1). Involved muscles, temporal distribution, synchronization, relation to motor activity, and stimulus sensitivity can be observed and categorized clinically and may direct diagnostic procedures for neuroanatomical and etiological categorization, which assists the choice of treatment(Shibasaki,2002) (Table 1).

The EMG activity during myoclonus does usually not exceed 200 milliseconds and duration of <50 milliseconds represents epileptic myoclonus. The study of myoclonus begins with the clinical observation and examination. The neuroanatomical site of involvement, rhythmicity, periodicity, stimulus sensitivity, mode of effective triggers, accompanying clinical signs, and specific electrophysiologic and neuroimaging patterns are important features that help consolidating the diagnosis.

3. Etiological classification of myoclonus

3.1. Symptomatic myoclonus in the ICU

A large variety of critical illnesses, medication, and illicit drugs may be associated with different types of myoclonus (Table 2).

Myoclonus can be triggered or aggravated by a large number of different drugs used in intensive care including opioids, such as hydromorphone(Babul and Darke,1992; Patel et al.,2006), morphine(Potter et al.,1989), fentanyl(Stuerenburg et al.,2000), non-steroidal anti-inflammatory drugs(Bandelot and Mihout,1978), neuroleptics(Pedavally et al.,2014; Strachan and Benoff,2006; Vural and Tezer,2012), antiepileptic drugs in high doses, such as carbamazepine(Magaudda and Di Rosa,2012), oxcarbazepine(Fanella et al.,2013), lamotrigine(Algahtani et al.,2014), topiramate(Miller et al.,2010), pregabalin and gabapentin(Ege et al.,2008; Healy et al.,2009; Hellwig and Amtage,2008), phenytoin(Duarte et al.,1996), and valproic acid(Gardner et al.,2009), antidepressants(Caviness and Evidente,2003; Evidente and Caviness,1999; Praharaj et al.,2010), the amino acid precursor of dopamine - levodopa(Yoshida et al.,1993) and bromocriptine(Buchman et al.,1987), antibiotics such as imipenem(Frucht and Eidelberg,1997), cefepime(Fugate et al.,2013), penicillin(Sackellares and Smith,1979), gentamycin(Sarva and Panichpisal,2012), ciprofloxacin(Jayathissa et al.,2010), piperazine(Kompf and

Neundorfer,1974), antihistamines(Irioka et al.,2008), and chemotherapeutics(Denison and Alghzaly,2006; Savica et al.,2011; Wyllie et al.,1997). Some anesthetics have also been associated with the emergence and aggravation of myoclonus including etomidate(Laughlin and Newberg,1985; Lumley and Morgan,1985), propofol(Tam et al.,2009), and enflurane(Ng,1980). In contrast, deep anesthesia and muscle relaxants may attenuate myoclonus. Additional substances that may trigger myoclonus are heavy metals including aluminium(Russo et al.,1992), bismuth(Teepker et al.,2002), lead(Hansen and Sharp,1978), manganese(Ono et al.,2002), and the use or withdrawal of illicit drugs, such as cocaine(Scharf,1989), tetrahydrocannabinol(Lozsadi et al.,2004), and alcohol(Drake,1983). Most drug-related myocloni are generated from the cerebral cortex with or without involvement of subcortical structures.

Aside from illicit drugs and medication, cortical myoclonus can emerge with critical illnesses including epilepsy, particularly with epilepsia partialis continua(Lim et al.,2004), nonconvulsive seizures and status epilepticus (Fernandez-Torre and Diaz-Castroverde,2004; Sutter et al.,2012), and progressive myoclonus epilepsy(Berkovic et al.,1991). Epileptic myoclonus can be the only seizure manifestation, one component of seizure related symptoms, or a more stable condition that is manifested in a non-paroxysmal fashion mimicking other movement disorders. This complex correlation is more obvious with epilepsia partialis continua (EPC) in which cortical myoclonus and overt focal motor seizures start in the same cortical area. In the literature there are only few epilepsy syndromes reported in critically ill adult patients with myoclonus such as EPC, nonconvulsive seizures, or status epilepticus(Sutter et al.,2012).

Myoclonus can also be linked to severe hypoxic brain injury after cardiac arrest (posthypoxic myoclonus)(Werhahn et al.,1997; Wijdicks et al.,1994) or to mild

hypoxic brain injury or decompression sickness (caisson disease) with restoration of consciousness (i.e., Lance-Adams syndrome)(Lance and Adams,1963; Yamaoka et al.,1994). The differentiation between myoclonus from severe hypoxic-ischemic brain injury and Lance-Adams syndrome and their different impact on outcome will be discussed below. Additional critical medical conditions associated with subcortical myoclonus are metabolic encephalopathies seen in patients with severe uremia(Artieda et al.,1992; Stark,1981; Tedeschi et al.,1982), liver failure(Butz et al.,2014), with infectious, autoimmune, or paraneoplastic encephalitides (Table 2), with heatstroke-related brain injury(Bazille et al.,2005), or with the posterior reversible encephalopathy syndrome(Boland et al.,2012). Less frequent critical illnesses that can present with myoclonus are HIV encephalopathy(Canafoglia et al.,2003; Kanjanasut et al.,2010) and prion diseases, such as Creutzfeldt-Jakob disease(Binelli et al.,2010; Chen et al.,2010). Myoclonus generated from spinal cord segments can be associated with traumatic spinal cord injury(Calancie,2006), spinal cord tumors(Massimi et al.,2009), the stiff man syndrome (Meinck et al.,1995), and with the progressive encephalomyelitis with rigidity and myoclonus (PERM)(Kraemer and Berlitz,2008; Kyskan et al.,2013; Shugaiv et al.,2013; Spitz et al.,2004). Peripheral myoclonus is typically associated with lesions of the peripheral nerves(Assal et al.,1998; Hudson et al.,2013).

3.2. Potential misinterpretation of non-ICU-related myoclonus

The etiologies of non-ICU-related myoclonus (including physiologic myoclonus, hereditary and epileptic myoclonus, and psychogenic myoclonus) differ from ICU-related myoclonus. Although these types of myoclonus are rarely seen in the ICUs, awareness and recognition of typical non-ICU-related myoclonus can avoid inadequate treatment escalation.

The most frequent physiologic myoclonic jerks are compiled in Table 1. Startle, a stereotypical myoclonic response to stimuli(Bakker et al.,2006), hiccups, and sleep onset myoclonus are distinctive and need to be distinguished from non-physiologic myoclonus in intensive care. Multifocal appearances can be misinterpreted as myoclonus from metabolic or hypoxic related brain dysfunction, and bilaterally synchronous myoclonus can resemble discharges from the brainstem reticular formation or cortical discharges from epileptic seizures.

Although autosomal-dominantly inherited syndromes are rare and more frequently seen in outpatients (Table 1), they should be considered in critically ill patients without other plausible causes and family history should be screened. Hereditary myoclonic-dystonia begins in childhood, and may be combined with psychiatric symptoms(Nardocci,2011). Typically, alcohol and activities such as walking and concentrating during reading reduce the jerks. In hereditary hyperekplexia, brisk and generalized startle emerges after acoustic or tactile stimulation without habituation to repeated stimulation or attenuation with pre-warning(Bakker et al.,2006). In a study of 9 patients and 20 controls, the head retraction reflex, described as a vestigial withdrawal reflex elicited by taps to the midline of the face, is characteristic in hereditary and acquired hyperekplexia(Tijssen et al.,1997b). According to a study of 28 patients, it may also be encountered in a variety of disorders, such as basal ganglia disease, amyotrophic lateral sclerosis, and the stiff person syndrome (Berger and Meinck,2003; Sandyk,1982).

Myoclonus during syncope is difficult to separate from seizures, as shown in a videometric analysis of 56 episodes of transient cerebral hypoxia. In contrast to epileptic myoclonus, syncope related myoclonus appears multifocal(Lempert et al.,1994) after the individual has fallen, and lasts 1-16 seconds. The recognition of myoclonus associated with transient cerebral hypoxia is important in the context of

critically ill patients, as during intensive care, patients can suddenly develop episodes of severe arterial hypotension that (if detected early) can be treated with vasopressors to avoid hypoxic brain injury.

Distinguishing psychogenic from somatic myoclonus is challenging calling for exclusion of somatic diseases. In a case series of patients with psychogenic myoclonus, >50% had segmental, almost 40% had generalized, and 5% had focal myoclonus (Monday and Jankovic, 1993). Stress and anxiety precipitated and exacerbated the jerks in 80%. The combination of the following clinical characteristics helps uncovering the psychogenic nature of myoclonic jerks: clinical features incongruous with "organic" myoclonus, evidence of psychopathologies, improvement with distraction, and the presence of incongruous sensory loss or false weakness. However, distinguishing somatic from psychogenic myoclonus can be difficult, especially in patients with movements that resemble propriospinal myoclonus. Detection of a „Bereitschaftspotential“ by EEG-EMG back averaging analysis (technique discussed below) and exclusion of spinal lesions on brain imaging can be helpful in differentiating between these two entities. Hence, advanced electrophysiological techniques and neuroimaging are invaluable in establishing the psychogenic origin of jerky movements in addition to the clinical features.

3.3. The neuroanatomical classification

The allocation of specific types of myoclonus in the ICU to involved neuroanatomical structures is essential to direct treatment. Table 3 compiles important clinical differences between cortical, subcortical, spinal, and peripheral myoclonus.

3.3.1. Cortical myoclonus in the ICU

Cortical myoclonus can be stimulus sensitive and elicited by tendon taps or touching, by posturing, passive or volitional movements, and by emotional excitation. However, stimulus sensitivity can be absent or difficult to identify clinically. Myoclonus of cortical origin appears as positive or negative myoclonus independently of each other or in combination (Shibasaki and Hallett, 2005) and is observed in many critical illnesses (Table 2) such as progressive myoclonus epilepsy (Berkovic et al., 1991), EPC (Lim et al., 2004), hypoxic brain injury (Lance and Adams, 1963; Werhahn et al., 1997; Wijdicks et al., 1994; Yamaoka et al., 1994), intoxication, metabolic or drug-related encephalopathies (Artieda et al., 1992; Stark, 1981; Tedeschi et al., 1982). The latter two are also linked to subcortical myoclonus (Chen et al., 2010; Hansen and Sharp, 1978; Ono et al., 2002; Teepker et al., 2002). Drugs associated with the emergence of (mostly cortical) myoclonus are described above and presented in Table 2.

In contrast to non-cortical myoclonus, cortical myoclonus may progress into convulsive seizures or status epilepticus regardless of etiology (Obeso et al., 1985). Often, the cortical nature of myoclonus cannot be determined clinically calling for an electrophysiological workup.

Treatment responsiveness and prognosis of cortical myoclonus are primarily determined by the etiology. Potentially reversible conditions include intoxication, drug-related encephalopathies, and myoclonus in association with epilepsies. Intoxication related myoclonus can often be treated by stopping the offending drugs or by gastric lavage. Myoclonus in association with epilepsies can respond to antiepileptic treatment, and myoclonus related to metabolic encephalopathies can ameliorate once the metabolic derangement can be controlled. In contrast, myoclonus associated with prion diseases (Centers of Disease Control and Prevention, 2015) and hypoxic brain injury is usually treatment refractory and linked to

a high mortality of up to 100%(Stevens and Sutter,2013). However, in a recent study of patients with myoclonus after hypoxic brain injury, 9% had good functional outcomes (Cerebral Performance Category 1–2), mainly patients without associated epileptiform activity(Seder et al.,2015). Hence, myoclonus of itself should not be considered a certain sign of adverse outcome in this context. Table 4 compiles the current evidence of the prognostic value of myoclonus in patients with hypoxic-ischemic encephalopathy. The differentiation between myoclonus from severe hypoxic brain injury and the more benign and mostly multifocal action and stimulus-sensitive myoclonus in Lance-Adams syndrome is crucial, as the latter is mostly linked to a favorable neurofunctional outcome(Lance and Adams,1963; Yamaoka et al.,1994). In contrast to severe postanoxic encephalopathy where the patients' mental status persists as comatose, the majority of patients with Lance-Adams syndrome regain consciousness. Some reports suggested that “giant” somatosensory evoked potentials (“giant” SSEPs described below), usually seen in patients with cortical myoclonus can distinguish patients with severe postanoxic encephalopathy from Lance-Adams syndrome. However, there are also reports describing “giant” SSEPs in patients with Lance Adams syndrome(Werhahn et al.,1997). Myoclonus in the Lance-Adams syndrome usually develops later (several days to months after the insult) than myoclonus from severe hypoxic-ischemic encephalopathy and persists without an EEG correlate. In contrast, myoclonus with severe hypoxic encephalopathy usually occurs within two days after cardiorespiratory arrest(English et al.,2009). Cerebral neuroimaging studies are not useful for the diagnosis of Lance-Adams syndrome with the exception of brain single photon emission computed tomography (SPECT) and brain positron emission tomography (PET). Compared with control groups, patients with Lance-Adams syndrome have increased glucose metabolism in the pontine tegmentum, mesencephalon, and

ventrolateral thalamus on PET(Frucht et al.,2004) and hypoperfusion in the temporal lobe on brain SPECT(Zhang et al.,2007).

3.3.2. Subcortical myoclonus in the ICU

Subcortical myoclonus includes periodic, dystonic, and reticular reflex myoclonus, startle syndrome, and palatal tremor (formerly palatal myoclonus)(Shibasaki and Hallett,2005). Whether palatal jerks represent myoclonus has been controversial. The term “palatal tremor” is used more often, because of the particularly rhythmic and non-“shock-like” jerks (discharge duration >200 milliseconds). The only clinical context in which symptomatic palatal tremor can be seen in the ICU is in patients with lesions in the Guillain-Mollaret triangle or the cerebellum, involving the levator palatine muscle(Deuschl et al.,1994). In this context, the palatal tremor is often accompanied with ocular or limb movements. In contrast to symptomatic palatal tremor, essential palatal tremor involves the tensor veli palatini leading to “clicks” in the ears(Shibasaki and Hallett,2005), which stops during sleep.

Subcortical myoclonus in the ICU is seen with intoxication, in patients with uremic (Artieda et al.,1992; Stark,1981; Tedeschi et al.,1982) or hepatic encephalopathy (Butz et al.,2014), with heatstroke-related brain injury(Bazille et al.,2005), and in association with the serotonin syndrome (Table 2), a clinical triad of 1) changes in mental-status with agitation, hypervigilance, delirium, and seizures, 2) autonomic hyperactivity with shivering, diaphoresis, mydriasis, hypertension, and tachycardia, and 3) neuromuscular abnormalities including myoclonus, tremor, hyperreflexia, clonus, and rigor(Boyer and Shannon,2005). These isolated features are unspecific, but their combination together with metabolic acidosis, rhabdomyolysis, elevated serum aminotransferase levels and creatinine, renal failure, and disseminated intravascular coagulopathy, complement the clinical picture. Subcortical myoclonus

can also emerge in association with the posterior reversible encephalopathy syndrome(Boland et al.,2012), a rare and potentially reversible breakdown of the cerebral circulatory autoregulation(Hinchey et al.,1996), often associated with (pre-)eclampsia or severe arterial hypertension, and less frequently with sepsis, Guillain-Barré syndrome-related autonomic dysregulation, autoimmune connective tissue disorders, chemotherapy, and organ transplantation. Precursors include vasospasm, vasculitis, and serum hyperviscosity(Hinchey et al.,1996). Subcortical myoclonus may also emerge from subacute sclerosing panencephalitis and resembles dystonia with jerks every 4-13 seconds(Shibasaki and Hallett,2005).

Reticular reflex myoclonus, a bilateral synchronous myoclonus generated from the reticular formation of the medulla oblongata, is seen after hypoxic brain injury (Table 2). Typically, the sternocleidomastoid and trapezius muscles, and the more rostral (facial) and caudal muscles (limbs) are involved(Hallett et al.,1977).

3.3.3. Spinal myoclonus in the ICU

Spinal myoclonus occurs spontaneously and involves muscles innervated by spinal segments. Typically, it is stimulus insensitive and presents with irregular or pseudo-periodical repetitions at high frequencies involving flexors of the trunk, hips, and knees. In contrast, the less frequent, slowly repetitive spinal myoclonus is stimulus sensitive. In the ICU, spinal myoclonus can emerge in association with tumors(Massimi et al.,2009), trauma of spinal cord segments(Calancie,2006), with spinal/intrathecal administration of anesthesia(Zamidei et al.,2010), or with autoimmune diseases including the stiff person syndrome most commonly associated with GAD65 antibodies(Meinck et al.,1995) (Table 2). Sometimes, the involved spinal segments spread in both directions rostrally and caudally, probably conducted through propriospinal tracts(Brown et al.,1994). Spinal myoclonus also

occurs with the stiff person syndrome plus, an autoimmune disease mediated by glycine receptor-antibodies or dipeptidyl peptidase-like protein 6(DPPX)-antibodies and characterized by progressive muscle rigidity, abnormal postures, spasms, and myoclonus(Balint et al.,2014; Carvajal-Gonzalez et al.,2014; Shugaiv et al.,2013).

3.3.4. Peripheral myoclonus in the ICU

Peripheral myoclonus is rare and usually caused by lesions of the plexus, nerves, roots, or rarely by anterior horn cell disease(Hudson et al.,2013) and nerve blocks(Hudson et al.,2013), possibly altering sensory inputs and inducing central reorganizations (Table 2)(Assal et al.,1998). Peripheral myoclonus is stimulus insensitive with jerks of 200 milliseconds with hemifacial spasm being the most common example.

4. The differential diagnoses of myoclonus in the ICU

Despite its typical phenomenology and increasing observations in critically ill patients, myoclonus can be missed or mistaken as physiologic (Table 1) or as other movement disorders seen in the ICUs such as spasms, clonus, and tremor.

4.1. Spasms

There is a smooth transition between myoclonus and spasms. While myoclonus is a brief and abrupt simple muscle contraction of milliseconds, spasms are more complex but stereotypic movements with fast peaks of action (milliseconds or seconds), followed by longer de-escalation phases (seconds or minutes). In contrast to myoclonus, spasms are triggered by muscle stretching or cutaneous stimulation.

4.2. Clonus

Clonus is an iteration or burst of triggered and maintained involuntary proprioceptive reflexes consisting of rhythmic series of muscle twitching(Wallace et al.,2005).

Rhythmicity is the main feature allowing the distinction from myoclonus. Clonus is particularly associated with lesions of the upper motor neuron involving descending motor pathways, and in many cases is, accompanied by spasticity.

4.3. Tremor

Tremor can be misinterpreted as myoclonus as it is an involuntary rhythmic and oscillating movement(Jankovic and Fahn,1980), sometimes only detectable by EMG. Unlike myoclonus, tremor may show rhythmic episodes of alternating contractions of agonist and antagonist muscles. Sometimes myoclonus can appear to be regular which can be described as “cortical tremor”.

5. ICU-related interferences with myoclonus

During intensive care, several factors may interfere with the typical appearance of myoclonus. Injuries of the central or peripheral nervous system and involved muscles may impede the emergence of myoclonus. Treatment-related interferences result from several drugs that are frequently used in intensive care as mentioned above (Table 2). While some anesthetics can trigger or aggravate myoclonus including etomidate (Laughlin and Newberg,1985; Lumley and Morgan,1985), propofol (Tam et al.,2009), and enflurane (Ng,1980), deep anesthesia and muscle relaxants attenuate myoclonus.

Artifacts from a variety of electrical ICU-devices, including electric beds, electronic infusion devices, or pacemakers may also impede the performance and proper interpretation of electrophysiological exams. Neurophysiologic examination including

electromyography, electroencephalography, or somatosensory evoked potentials can be limited by bandages or wounds that impeded electrode placements. Potentially disturbing reversible factors need to be recognized prior to proper clinical and neurophysiological examination of myoclonus. This includes weaning the patients from interfering drugs and inactivating electrical devices not essential for immediate life-support.

6. Electrophysiology

6.1. *Electromyography*

Digital EMG of muscle discharges helps distinguishing myoclonus from other involuntary movements (tremor or dystonia). EMG is recorded with skin electrodes placed 2-3 cm apart overlying the muscles of interest and a simultaneous recording from several muscles to demonstrate the distribution and spread of myoclonus (Shibasaki and Hallett, 2005).

Cortical myoclonus shows EMG correlates <50 milliseconds (Figure 1) involving agonist and antagonist muscles synchronously, whereas subcortical myoclonus exceeds 50 milliseconds. However, short EMG discharges can also be associated with brainstem reflex myoclonus (Hallett et al., 1977). In critically ill patients, positive cortical myoclonus usually occurs irregularly. Rhythmic patterns exist in non-critically ill patients seen outside the ICUs, such as familial cortical myoclonic tremor (Brown and Marsden, 1996) and corticobasal degeneration (Carella et al., 1997). Negative myoclonus can be identified clinically, but EMG recorded during isometric muscle contraction helps confirming the diagnosis (Figure 1). In CJD, myoclonus can be stimulus sensitive or (more frequently) spontaneous, stimulus insensitive and pseudo-periodically in resting conditions with intervals of 600-1,500 milliseconds (Shibasaki and Hallett, 2005).

Subcortical myoclonus, as typically seen with subacute sclerosing panencephalitis, is linked to stereotyped slow EMG discharges occurring periodically at 4-13 seconds (Shibasaki and Hallett, 2005).

In spinal myoclonus, EMG should be recorded from multiple muscles to detect simultaneous contractions of muscles innervated by the same spinal segment and to uncover spreads from a certain spinal segment to rostral and/or caudal segments over ~10 meters/seconds with propriospinal myoclonus (Shibasaki and Hallett, 2005). In peripheral myoclonus rhythmic contractions last 200-400 milliseconds (Assal et al., 1998).

6.2. *Electroencephalography*

Digital EEG should be recorded with electrodes over the central areas, as cortical myoclonus typically derives from the sensorimotor cortex (Shibasaki and Hallett, 2005) showing multifocal or generalized spike-and-wave or poly-spike-wave discharges (Artieda et al., 1992; Baumgartner et al., 1996). In non-cortical myoclonus, jerk-linked discharges are absent.

Combined real-time EEG and EMG provide information regarding the relationship between the myoclonus and brain activities. The EEG-EMG polygraphy should be performed first, as it is the most effective, and time-efficient technique revealing involved muscle groups and correlating cortical discharges.

6.3. *Electroencephalographic-electromyographic polygraphy*

The EEG-EMG polygraph is the simultaneous recording of EEG and EMG to investigate cortical discharges that are present in cortical myoclonus (Figure 2) or absent in myoclonus with other neuroanatomical origins. This technique enables jerk-locked back averaging and evoked potential studies combined with recording of the

long-latency and long-loop reflexes(Shibasaki and Hallett,2005). Jerk-locked back averaging enables to back average the simultaneously recorded EEGs with respect to myoclonus. EMG recorded jerks should be further investigated by EEG with scalp electrodes over the respective motor-area. Usually multiple (up to 50) sweeps are recorded and superimposed to increase the contrast uncovering myoclonus-related cortical brain activity that otherwise would be missed(Shibasaki and Hallett,2005). This technique is particularly important in patients with cortical myoclonus where spikes at the central electrodes correspond somatotopically to the involved muscle. Usually, extensive electrophysiologic investigations of reticular reflex myoclonus following hypoxic brain injury with EEG-EMG-polygraphy is not performed, as evidence of structural brain damage provided by magnetic resonance imaging, absent or late N20 potentials on SSEPs, and persistent coma sufficiently proof severe brain injury and represent strong outcome predictors(Stevens and Sutter,2013). The cortical spikes identified with jerk-locked back averaging do not represent the origin of myoclonus, but the retrograde transmissions of impulses generated in the reticular formation of the brainstem.

In patients with subacute sclerosing panencephalitis the quasi-periodic myoclonus is linked to high-amplitude (200-600 uV), long-duration (500-2000 milliseconds) EEG (“Radermacker”)–complexes which are pathognomonic for the disease together with the long discharge interval of 4-13 seconds(Celesia,1973; Praveen-kumar et al.,2007).

6.4. Somatosensory evoked potentials

For SSEPs, the median nerve is stimulated at the wrist with square-wave impulses of 0.2-0.5 milliseconds at 1-2 Hz with 10-15% above the motor threshold. Sometimes, with cortical reflex myoclonus, identification of the motor threshold is difficult by visual

inspection because of significantly lowered threshold of the long-latency reflex that may obscure the direct motor response. Long-loop reflexes are automatic motor responses to somatosensory stimuli that are believed to operate via the cerebral cortex (“transcortical reflexes”). However, long-loop reflexes occur at latencies too long to be explained with the mediation by segmental spinal cord circuits yet too short to be clearly mediated volitionally.

SSEPs of cortical reflex myoclonus show waveforms with enlarged early cortical components (Shibasaki and Hallett, 2005). These pathognomonic “giant” potentials (10 times as large as normal (Hitomi et al., 2006), or >10 uV with medianus-SSEP P25-N35) can be distinguished and support the clinical diagnosis of cortical or cortical reflex myoclonus.

The short-latency SSEP components, which occur subcortically before 20 milliseconds, are not enhanced in any type of myoclonus. Hence, the differentiation of subcortical from other types of myoclonus is not possible by SSEP (Shibasaki and Hallett, 2005).

In reticular reflex myoclonus after hypoxic brain injury, the long-latency reflex, which is thought to be mediated by the spinal cord, is enhanced, but not cortical evoked potentials. However, there is a great inter-individual variability of reflex latency, indicating the necessity for looking at individual responses to a single stimulus rather than averaging (Shibasaki and Hallett, 2005).

7. Neuroimaging

Although there is no specific neuroimaging correlate of myoclonus, brain imaging should be performed to exclude or identify imaging patterns related to underlying diseases. In the following section we will limit our review on data from magnetic resonance imaging (MRI), as computed tomography does not reveal specific

changes in most cases. Other neuroimaging techniques, such as magnetic resonance spectroscopy, positron emission tomography, and single photon emission computed tomography are not well studied.

The diagnostic yield of neuroimaging is studied best in adult patients with hypoxic brain injury following cardiac arrest (Table 5) with multifocal cortical or white matter changes on brain MRI (Figure 3).

In patients with prolonged status epilepticus, brain MRI may also reveal hyperintensities mainly restricted to the seizing cortical areas and subcortical grey matter that may resemble changes from hypoxic brain injury (Cartagena et al., 2014; Cianfoni et al., 2013).

In myoclonus from encephalitides, only few cases are described in the literature. The MRI can show a variety of abnormalities that depend on the underlying cause of encephalitis. Patients with myoclonus emerging with Herpes Simplex virus encephalitis may show hyperintensities with slight edema in the bilateral temporal and insular cortices and right thalamus on the T2-weighted and fluid attenuation inversion recovery (FLAIR) images of brain MRI (Park et al., 2011). In patients with Epstein-Barr virus meningo-encephalitis that presented with pharmacoresistent myoclonus, the MRI showed a high signal in the leptomeninges, especially in the bilateral parietal sulci (Lee et al., 2014). However, in patients with West Nile virus encephalitis induced opsoclonus-myoclonus syndrome (Cooper and Said, 2014) and patients with opsoclonus-myoclonus syndrome associated with mumps virus infection (Kang and Kim, 2014), the MRI is mostly normal. In patients with myoclonus from subacute sclerosing panencephalitis, brain MRI revealed punctuate hyperintensities in subcortical and periventricular deep white matter in both cerebral hemispheres (Sharma and Biswas, 2013). MRI studies in patients with HIV-related opsoclonus–myoclonus–ataxia syndromes does not reveal significant

abnormalities(Kanjanasut et al.,2010).

Aside from neuroimaging studies in patients with infectious encephalitides, several cases have been reported of patients with paraneoplastic encephalitis presenting with opsoclonus-myoclonus-like syndrome and stiff-person syndrome. However, brain MRI is mostly reported to be normal(Kumar et al.,2005; Mukherjee et al.,2004; Thumen and Moser,2010) and only few cases note multiple nonspecific nonenhancing areas of signal abnormality involving the cortex of both cerebral hemispheres(Rickman et al.,2000). While brain MRI in encephalomyelitis with rigidity and myoclonus (PERM) can reveal numerous small foci of high T2 FLAIR in the subcortical, deep and periventricular white matter of the cerebral hemispheres bilaterally(Kyskan et al.,2013), other cases are reported without abnormalities on neuroimaging(Kraemer and Berlitz,2008; Spitz et al.,2004). MRI of the spine did not demonstrate any significant abnormalities. In another case with an anti-ri-antibody-associated paraneoplastic syndrome in a man with breast cancer, the brain MRI showed a reversible pontine lesion(Kim et al.,2009).

In steroid responsive encephalitis with autoimmune thyroiditis, MRI abnormalities and myoclonus were seen in a study of 80 patients(Yoneda,2012).

Neuroimaging studies in patients with myoclonus associated with metabolic derangements are rare. Although changes on brain MRI in patients with uremia or liver failure are well described, our search of the literature could not find any reports of brain MRI findings in this context.

Rarely, patients are reported to present with opsoclonus-myoclonus syndrome showing signs of a posterior reversible encephalopathy syndrome on brain MRI(Boland et al.,2012) (Figure 4).

8. Treatment of myoclonus in the ICU

In multifocal cortical myoclonus, treatment of the underlying disease is most effective.

In patients with multiple drugs, the discontinuation of medication and treatment of metabolic derangements may resolve myoclonus. In most critically ill patients, however, myoclonus persists and may harm the patients. Before antimyoclonic treatment is started, fixation of extremities or medical devices to the body is needed, as abrupt movements may accidentally pull out intravenous lines or endotracheal tubes.

Treatment of symptomatic myoclonus is challenging. Often high drug doses are needed that can frequently lead to side-effects. Drugs that are effective in some patients may worsen symptoms in others. Because of the low level of evidence, therapeutic options rely on expert opinions(Dijk and Tijssen,2010). Although some drugs have limited effects, they may be more efficient when combined with drugs acting on different pathways. Figure 5 summarizes treatment options for the different types of myoclonus.

8.1. Treatment of cortical myoclonus

Cortical myoclonus responds well to antiepileptic drugs. Levetiracetam is recommended as first-line treatment and additional high dosed piracetam may have antimyoclonic effects. However, the latter is not available in many countries including North America. Valproic acid is recommended as second-line medication. These drugs are recommended not only because of their antimyoclonic effects, but also because they do not significantly alter consciousness. If sedating effects are not critical or patients are mechanically ventilated, benzodiazepines may be titrated until antimyoclonic effect is reached. In posthypoxic cortical reflex myoclonus, clonazepam and valproic acid were recommended before levetiracetam became

broadly available(Obeso et al.,1989). Mostly, a combination of drugs is needed for successful treatment. In a study of patients with Lance-Adams syndrome clonazepam, valproate, and piracetam were effective in treating approximately half of the patients(Frucht and Fahn,2000). Other opinion leaders recommend levetiracetam, zonisamide, clonazepam, and valproate as the first treatments of choice(Polesin and Stern,2006).

8.2. Treatment of subcortical myoclonus

Antiepileptic drugs are mostly ineffective. Brainstem myoclonus is often treatable with clonazepam(Tijssen et al.,1997a), and L-5-hydroxytryptophan can be effective for reticular reflex myoclonus(Obeso,1995).

In the opsoclonus-myoclonus syndrome, treatment of the underlying disease with rituximab, adrenocorticotrophic hormones, or intravenous immunoglobulin therapy is recommended(Dijk and Tijssen,2010) if not intoxication-related.

In myoclonus dystonia, clonazepam and trihexyphenidyl can be effective. In addition L-5-hydroxytryptophan (a serotonin precursor) is recommended, but side-effects are frequent. To prevent conversion to serotonin, L-5-hydroxytryptophan should be used with a decarboxylase inhibitor, which might limit side-effects(Dijk and Tijssen,2010). However, L-5-hydroxytryptophan is not available in many countries. Alternatively, sodium oxybate, levodopa, zolpidem, levetiracetam, piracetam, and deep brain stimulation of the globus pallidus interna are reported to be effective(Gerschlager and Brown,2009).

8.3. Treatment of spinal myoclonus

Treatment of the underlying cause is crucial, as symptomatic therapy is often disappointing. With propriospinal myoclonus many patients have psychogenic

myoclonus calling for psychiatric intervention(van der Salm et al.,2014) together with clonazepam as the first-line drug for segmental and propriospinal myoclonus.

Alternatively, zonisamide can be effective for propriospinal myoclonus(Dijk and Tijssen,2010).

8.4. Treatment of peripheral myoclonus

Pharmacological treatment is mostly disappointing, but botulinum toxin may be effective, especially for hemifacial spasm(Dijk and Tijssen,2010).

9. Conclusions

Myoclonus can emerge with many critical illnesses, but may resemble physiologic and other pathologic involuntary movements. Central or peripheral neurologic injuries, anesthetics, and muscle relaxants interfere with the typical appearance of myoclonus. Identifying “real myoclonus” in critically ill patients, determining the neuroanatomical origin, and distinguishing between myoclonus associated with critical and non-critical illnesses is essential to direct adequate treatment. The recognition of cortical myoclonus is critical, as this myoclonus is treatable and may progress to generalized convulsive seizures or status epilepticus regardless of etiologies. However, the neuroanatomical origins and pathophysiological mechanisms cannot be reliably determined by clinical observation alone calling for heightened awareness and a rigorous use of neurophysiological and neuroimaging examinations.

The combination of clinical, electrophysiological and neuroradiological examinations reliably uncovers the neuroanatomical sources and pathophysiological mechanisms of myoclonus.

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Figure Legends

Figure 1: Schematic illustration of electromyographic correlates of positive and negative myoclonus during sustained muscle contraction.

Figure 2: Electroencephalogram–electromyogram (EEG–EMG) polygraphic records in a patient with progressive myoclonus epilepsy manifesting positive myoclonus in the hands at rest. Note that most myoclonic jerks are associated with a spike-and-wave complex on EEG. EEG recorded in reference to ipsilateral earlobe electrode, and negativity shown upward. ECR, extensor carpi radialis muscle; 1st DI, first dorsal interosseous muscle; Rt, right (reproduced from Shibasaki and Hallett, 2005 with kind permission from John Wiley and Sons).

Figure 3: Hypoxic-ischemic encephalopathy with hyperintense thalami and cortical grey matter of a patient with cortical myoclonus (Serial axial diffusion weighted imaging; on 1.5-T MRI).

Figure 4: Posterior reversible encephalopathy syndrome (PRES) with widespread confluent subcortical hyperintensities in the posterior circulation of a patients with myoclonus following hypertensive crisis (Serial axial FLAIR; on 1.5-T MRI).

Figure 5: Current recommendations of pharmacotherapy for myoclonus according to the neuroanatomical origin (based on and adapted from (Dijk and Tijssen, 2010)).

*Polytherapy with 3-4 drugs is more effective than monotherapy, particularly for cortical myoclonus.

DBS = deep brain stimulation.

Table 1: The classification of myoclonic movements (based on the work of S. Fahn et al. (Dijk and Tijssen,2010; Fahn,2002))

Clinical classification	Etiological classification	Neuroanatomical classification
Involved muscle groups Temporal distribution Synchronization Relation to motor activity Sensitivity to stimuli Positive or negative (“asterixis”)	Physiological myoclonus - Syncope related myoclonus - Startle - Hicups Sleep onset myoclonus Hereditary myoclonus - Hereditary myoclonic-dystonia - Hereditary hyperekplexia Epileptic myoclonus Symptomatic myoclonus (details in Table 2) Psychogenic myoclonus	Cortical myoclonus Subcortical myoclonus Spinal myoclonus Peripheral myoclonus

Table 2: Causes of symptomatic myoclonus and its neuroanatomical origin in adult ICU-patients

Neuroanatomical origin of myoclonus	Critical illness or exposures	Representative reference
Cerebral cortex (and sometimes subcortical)	Intoxication/drug related encephalopathy	
	Anesthetic drugs	Etomidate (Laughlin and Newberg,1985; Lumley and Morgan,1985) Propofol (Tam et al.,2009) Enflurane (Ng,1980)
	Opioids	Hydromorphone (Babul and Darke,1992; Patel et al.,2006)\ Morphine (Potter et al.,1989) Fentanyl (Stuereburg et al.,2000)
	Non-steroidal anti-inflammatory drugs	Diclofenac (Bandelot and Mihout,1978)
	Neuroleptic drugs	Haloperidol (Vural and Tezer,2012) Serotonin (Pedavally et al.,2014) Quetiapine (Strachan and Benoff,2006)
	Antiepileptic drugs	Carbamazepine (Magaudda and Di Rosa,2012) Oxcarbazepine (Fanella et al.,2013) Lamotrigine (Algahtani et al.,2014) Topiramate (Miller et al.,2010) Pregabalin and gabapentin (Ege et al.,2008; Healy et al.,2009; Hellwig and Amtage,2008) Phenytoin (Duarte et al.,1996) Valproic acid (Gardner et al.,2009)
	Antidepressants	Lithium (Caviness and Evidente,2003) Tricyclic antidepressants (Evidente and Caviness,1999), Clozapine (Praharaj et al.,2010)
	Dopamine agonists	Levodopa (Yoshida et al.,1993) Bromocriptine (Buchman et al.,1987)
	Cardiac medication	Diltiazem (Jeret,2002) Propafenone (Chua et al.,1994)
	Antibiotic drugs	Imipenem (Frucht and Eidelberg,1997) Cefepime (Fugate et al.,2013) Penicillin (Sackellares and Smith,1979) Gentamycin (Sarva and Panichpisal,2012) Ciprofloxacin (Jayathissa et al.,2010) Piperazine (Kompf and Neundorfer,1974)
	Antihistamines	Antihistamines (Irioka et al.,2008)
	Cytostatic drugs	Vidarabine (Vilter,1986)
	Chemotherapeutics	Busulfan (Denison and Alghzaly,2006) Chlorambucil (Wyllie et al.,1997) Ifosfamide (Savica et al.,2011)
	Heavy metals	Aluminium (Russo et al.,1992) Bismuth (Teepker et al.,2002) Lead (Hansen and Sharp,1978) Magnanese (Ono et al.,2002)
(Spinal cord with tetrahydrocannabinol)	Illicit drugs (or withdrawal)	Cocaine (Scharf,1989) Tetrahydrocannabinol (Lozsadi et al.,2004) Alcohol withdrawal (Drake,1983)
	Vascular-hypoxic encephalopathy	Myoclonus with severe hypoxic-ischemic encephalopathy (Werhahn et al.,1997; Wijdicks et al.,1994) Lance-Adams syndrome (Lance and Adams,1963; Yamaoka et al.,1994)
	Epilepsy	Epilepsia partialis continua (Lim et al.,2004) Nonconvulsive seizures and status epilepticus (Fernandez-Torres and Diaz-Castroverde,2004) Progressive myoclonus epilepsy (Berkovic et al.,1991)
	HIV encephalopathy	(Canafoglia et al.,2003; Kanjanasut et al.,2010)
	Metabolic encephalopathies	Uremic (Artieda et al.,1992; Stark,1981; Tedeschi et al.,1982) Hepatic encephalopathy (Butz et al.,2014) Rarely hyper- and hypoglycemic encephalopathy

	Prion diseases	Creutzfeldt-Jakob disease (Binelli et al.,2010; Chen et al.,2010)
(subcortical in SSPE, mumps and paraneoplastic encephalitis)	Encephalitides	Viral (HSV (Park et al.,2011) EBV (Lee et al.,2014) West Nile virus (Birlutiu and Birlutiu,2014; Cooper and Said,2014) SSPE (Sharma and Biswas,2013; Shibasaki and Hallett,2005) Mumps infections (Kang and Kim,2014) Autoimmune (Balint et al.,2013; DeFelipe-Mimbrera et al.,2014; Ghoreishi et al.,2013; Leigh et al.,1980; Smith et al.,2011; Stern et al.,2014; Uehara et al.,2011) Paraneoplastic (Berger and Mehari,1999; Kim et al.,2009; Kumar et al.,2005; Morales La Madrid et al.,2012; Mukherjee et al.,2004; Rickman et al.,2000; Thumen and Moser,2010)
Subcortical	Traumatic brain injury	(Birbamer et al.,1993; Jacob and Chand,1999)
	Heatstroke	(Bazille et al.,2005)
	Posterior reversible encephalopathy syndrome	(Boland et al.,2012)
	Intrathecal anesthesia	(Zamidei et al.,2010)
Spinal cord	Traumatic spinal cord injury	(Calancie,2006)
	Spinal cord tumors	(Massimi et al.,2009)
	Stiff person syndrome	(Meinck et al.,1995)
	Progressive encephalomyelitis with rigidity and myoclonus (=stiff person syndrome plus)	(Kraemer and Berlitz,2008; Kyskan et al.,2013; Shugaiv et al.,2013; Spitz et al.,2004)
Peripheral nervous system	Peripheral nerve lesions	(Assal et al.,1998; Hudson et al.,2013)
Peripheral nervous system	Peripheral nerve blocks	(Hudson et al.,2013)

HSV = herpes simplex virus; EBV = Epstein-Barr virus; SSPE = Subacute sclerosing panencephalitis; HIV = human immunodeficiency virus

Table 3: The clinical differences between cortical, subcortical, spinal, and peripheral myoclonus

Neuroanatomical generator	Appearance with	Movement	Rhythmicity	Stimulus sensitivity
Cerebral cortex	Spontaneously or with movement (action myoclonus)	Shock-like	Irregular, but can be rhythmic	Highly sensitive
Cerebral subcortical structures	Spontaneously (brainstem)	Less shock-like	Periodic	Brainstem reflex myoclonus can be sensitive
Spinal cord	Spontaneously	Variable	Periodic or rhythmic	Can be sensitive
Peripheral nervous system	Spontaneously	Shock-like	Arrhythmic	Not sensitive

Table 4: The prognostic value of myoclonus in adult ICU-patients with hypoxic-ischemic brain injury

Study design	Time of examination of myoclonus	Definition of poor outcome	Predictive value of myoclonus regarding poor outcome	Reference
Prospective studies				
Study with 107 patients	After CPR	Death during hospital stay	- False-positive rate 0% - Sensitivity 43% - Specificity 100%	(Wijdicks et al.,1994)
Study with 407 patients	In first 3 days after CPR	Death or vegetative state at 1 month	- False-positive rate 0% - Sensitivity not provided - Specificity not provided	(Zandbergen et al.,2006)
Study with 111 patients	In the first 3 days after CPR and hypothermia	Death during hospital stay	- 7% with false-positive mortality predictions during hypothermia - Sensitivity 94% - Specificity 96%	(Rossetti et al.,2010)
Study with 103 patients	At day 3 after CPR and hypothermia	Death during hospital stay	- False-positive rate 0% - Sensitivity 8% - Specificity 100%	(Fugate et al.,2010)
Study with 61 patients	After CPR and hypothermia	CPC 3-5 at 3 months	- False-positive rate 7% - Sensitivity 21% - Specificity 93%	(Rossetti et al.,2012)
Study with 471 patients	After CPR and hypothermia	CPC 3-5 at discharge	- False-positive rate 9% - Sensitivity not provided - Specificity not provided	(Seder et al.,2015)
Systematic review				
Review including 12 studies	In the first 3 days after CPR hypothermia	Death or coma after 1 month or death, coma, or severe disability requiring nursing care after 6 months	- False-positive rate 0% - Sensitivity not provided - Specificity not provided	(Wijdicks et al.,2006)
Retrospective study				
Study with 37 patients	At day 3 after CPR and hypothermia	No recovery of awareness during hospital stay	- False-positive rate 0% - Sensitivity not provided - Specificity not provided	(Al Thenayan et al.,2008)

CPR = cardiopulmonary resuscitation; CPC = cerebral performance category

Table 5: Neuroimaging findings in adult ICU-patients with hypoxic-ischemic encephalopathy

Imaging technique & study design	Time of imaging after CPR	Neuroimaging patterns	Definition of poor outcome	Predictive value for poor outcome	References
Brain CT					
Prospective study	At a median 1 days after CPR and hypothermia	Global cerebral edema	Death in hospital	- False-positive rate 0% - Sensitivity 10% - Specificity 100%	(Fugate et al.,2010)
Brain MRI					
Prospective study	In the first 15 days after CPR	Diffuse signal abnormalities in the cortex and subcortical areas or effacement of the sulci	Death in hospital	- All 8 patients with these imaging patterns died; 1 of 2 patients who survived had subcortical ischemia - Sensitivity not provided - Specificity not provided	(Wijdicks et al.,2001)
Retrospective study	In first 7 days after CPR and hypothermia	Lower whole brain and regional median ADC	mRS 3-6 at 6 months	- Patients with mRS >3 had lower median whole brain and regional ADC - Sensitivity 41% - Specificity 100%	(Wu et al.,2009)
Prospective study	At a median 4.1 (good outcome) and 9.8 days (poor outcome) after CPR	Multilobar, or diffuse lesion pattern with cortical involvement on DWI and FLAIR	CPC 4-5 at discharge	- False-positive rate 0% - Sensitivity 88% - Specificity 100%	(Topcuoglu et al.,2009)
Prospective study	In the first 7 days after CPR with hypothermia	ADC <650x10 ⁶ mm ² /sec	Death in hospital	- False-positive rate 0% - Sensitivity 81% - Specificity 100%	(Wijman et al.,2009)
Prospective study	At 48 hours after CPR with hypothermia	Global ischemia or focal ischemia with total lesion volume >20mL on DWI	CPC 3-5 at 6 months	- False positive rate 0% - Sensitivity 77% - Specificity 92%	(Choi et al.,2010)
Prospective study	In the first 5 days after CPR with hypothermia	Cortical and/or deep grey nuclei lesions	Death at 6 months	- False positive rate 0% - Sensitivity 100% - Specificity 100%	(Cronberg et al.,2011)
Retrospective study	Between 1 and 150 days after CPR	Changes in large areas of the cerebral cortex and the deep grey matter on T2 and DWI	Death, profound cognitive impairment and persistent vegetative state, minimally area states or severe physical impairment at discharge	- False positive rate 0% - Sensitivity 41% - Specificity 60%	(Howard et al.,2012)
Prospective study	At a median of 166 minutes after CPR	Predefined brain regions were qualitatively scored on DWI according to severity of abnormality on a scale from 0-4	CPC 3-5 at discharge	- False positive rate 0% - Sensitivity 92-100% - Specificity 100%	(Park et al.,2015)

CT = computed tomography; MRI = magnetic resonance imaging; CPR = cardiopulmonary resuscitation; ADC = apparent diffusion coefficient; DWI = diffusion-weighted imaging; FLAIR = fluid attenuated inversion recovery

Outcome rating scales: CPC = Cerebral Performance Categories Scale; GOS = Glasgow Outcome Scale; mRS = modified Ranking Scale

Neuroanatomical origine

First-line

Second-line/alternatives*

Peripheral nerves

levetiracetam (up to 3 g/day),
piracetam (up to 20 g/day)

Hereditary cortical myoclonus:
clonazepam (up to 1 mg/day)

Posthypoxic cortical reflex
myoclonus:
clonazepam (up to 15 mg/day),
valproic acid (up to 2 g/day)

valproic acid (up to 2 g/day),
clonazepam
(up to 15 mg/day, if refractory and
patient is ventilated i.v. drip up to 100
mg/hour)

primidone, phenobarbital,
phenytoin,
L-5-hydroxytryptophan

Myoclonus dystonia:
clonazepam (up to 6 mg/day),
trihexyphenidyl (up to 6 mg/day)

Opsoclonus-myoclonus syndrome:
rituximab, ACTH, i.v.
immunoglobulins for 5 days,
clonazepam (up to 6 mg/d)

Hyperekplexia:
clonazepam (up to 6 mg/d)

Reticular reflex myoclonus:
L-5-hydroxytryptophan (up to 15
mg/day)

Palatal myoclonus:
clonazepam (up to 6 mg/d),
carbamazepine, phenytoin,
barbiturates, valproic acid, baclofen,
anticholinergics, tetrabenazine,
lamotrigine, sumatriptan, piracetam,
botulinum toxin

levodopa, L-5-hydroxytryptophan,
valproic acid, piracetam,
levetiracetam, zolpidem, DBS

tinnitus masking device

Segmental:
clonazepam (up to 6 mg/day)

Propriospinal:
clonazepam (up to 6 mg/day)

carbamazepine, tetrabenazine,
botulinum toxin

zonisamide

Botulinum toxin