Introduction

Sudden muscle contractions (positive) or muscle tone lapses (negative) that are brief, involuntary, and shock-like are defined as myoclonus. There are several conditions that can lead to myoclonus, and myoclonus can be classified according to clinical presentation/etiology, examination characteristics, or pathophysiology. In 1963, Lance and Adams described four patients with dysarthria, ataxia, and intention or action myoclonus that appeared a few days after the resolution of coma as a result of hypoxic encephalopathy. The presence of myoclonus after hypoxia had been mentioned before the description of Lance and Adams, but the syndrome had not been described in detail. Many cases have been described since 1963, and now the myoclonus that appears after the resolution of coma and is variably associated with dysarthria, ataxia, seizures, or cognitive deficits is now referred to as chronic post-hypoxic myoclonus (PHM) or Lance–Adams syndrome (LAS). However, not all myoclonus after hypoxia resembles LAS. Specifically, the myoclonus that occurs almost immediately after a hypoxic episode is called acute PHM. Moreover, we feel that it is prudent to differentiate between acute PHM and the myoclonus syndrome described by Lance and Adams, especially since the clinical characteristics, prognosis, and treatment are different. In addition, taking into account these clinical differences, the
mechanism and pathophysiology for acute PHM may also be different from LAS.4,5 Neurophysiological studies such as electromyography (EMG), electroencephalography (EEG), somatosensory evoked potential (SEP), back-averaged EEG transients, and long latency reflex are useful in finding the myoclonus generator.6,7 There has been limited reviewed information on the spectrum of neurophysiological findings seen in PHM types. A perspective on the whole spectrum of both acute and chronic PHM myoclonus (LAS) with attention to both clinical and neurophysiology findings is necessary to study pathophysiology and treatment of PHM. The aim of this review is to provide an up-to-date description of the literature and to discuss the whole spectrum of this unusual disorder, and to lessen the confusion between the two major types of PHM. We highlight clinical differences, neurophysiology findings, and treatment by reviewing the recently published reports for both PHM types.

**Methods**

We performed a systematic literature search of the PUBMED database using the terms “myoclonus,” “post-anoxic myoclonus,” “post-hypoxic myoclonus,” and “Lance–Adams syndrome.” The search was performed in December 2015 and included articles published in the English language from 1960 to 2015. This search strategy revealed more than 8,000 articles. The articles published in peer-reviewed journals and that reported myoclonus cases after hypoxia were included in the review. The majority of the articles were case reports and case series. Review articles were considered only if they included case reports or case series. We also reviewed relevant articles that were present in the reference lists of identified papers for added perspective.

**Acute post-hypoxic myoclonus**

Our search found 65 articles with acute PHM cases. Of these, 37 articles described findings with neurophysiological techniques. Out of 37, 10 were research studies and the others were case reports or case series. All 37 articles that reported neurophysiological findings are listed in Table 1. The myoclonus that appeared in comatose patients after hypoxic injury to the brain was usually generalized in nature, but multifocal myoclonus, periodic eye opening, swallowing movements, upward eye deviation, and flexion of the neck and trunk have been reported as well.8–11 Acute post-hypoxic generalized myoclonus usually appeared within 1 day of hypoxic injury, but the development of multifocal myoclonus may take up to 3 days.12 We found one case report where generalized myoclonus was described after 48 hours of hypoxic injury; the patient had been initiated on a neuromuscular blocking agent that could have masked the earlier appearance of myoclonus.13

Generalized acute PHM was usually present only for a number of days. The patients would usually deteriorate (with death), continue to a chronic vegetative state, or improve with or without LAS. Any such evolution was associated with the generalized myoclonus being transient. The appearance of generalized myoclonus after hypoxic injury to the brain is often considered to be a marker of poor prognosis.14,15 In a systematic review published by the American Academy of Neurology (AAN) in 2006, the appearance of “myoclonic status epilepticus” within 24 hours was considered to be a marker of poor outcome.15 The nature of PHM whether generalized or focal was not mentioned in some studies.16,17 If the myoclonus was generalized and continuous (>30 minutes duration), then it was referred to as “status myoclonicus.” However, there is a lack of consensus on the duration criterion of myoclonus in this instance and whether this occurrence constitutes a seizure. There are other terms that are used interchangeably for this particular presentation, including “myoclonic status epilepticus,” “status myoclonus,” and “myoclonic status.”11,18 Most studies included in this review were before the era of therapeutic hypothermia. Some studies that used hypothermia have been published where a good outcome has been reported despite the presence of myoclonus acutely after hypoxic injury.16,19,20 Since the introduction of therapeutic hypothermia, caution has been advised on using the presence of acute PHM as the sole criteria for prognosis.10,21,22 It is sometimes difficult to perform an accurate neurological examination and evaluate myoclonus because sedatives or neuromuscular blocking agents are used frequently in patients who undergo the hypothermia protocol.22 Hypothermia by itself can also lead to EEG changes, and reliable interpretation should be performed at a core temperature of more than 35°C.24

Neurophysiological findings in 741 cases from the 37 articles for acute PHM that were reviewed are included in Table 1. These neurophysiological findings seen in acute PHM are summarized in Figure 1. Neurophysiological observations are reported for acute PHM, but studies using EMG and other movement neurophysiological techniques among acute PHM cases were rare. As such, we found EEG to be by far the most common neurophysiology test used in acute PHM, perhaps because other neurophysiology techniques are not feasible under the circumstances. Indeed, the concern over possible seizures seems to drive the indication for EEG testing. There are several EEG findings described in acute PHM such as burst suppression pattern,14 electrographic status epilepticus,16 periodic epileptiform discharges,16 and diffuse slower frequencies.12 Surface EMG was performed in only one case and SEP was mentioned in two research studies for 51 cases. Specific patients could have more than one EEG pattern reported, since many patients demonstrated changing patterns on repeated EEGs during their clinical course after acute hypoxia, even while the myoclonus is present. The prevalence of specific EEG patterns out of 741 cases having EEG during clinical myoclonus was as follows: burst suppression (56%), spike-wave activity (both continuous and intermitent) (37%), myoclonic status epilepticus (clinical and electrographic) (31%), diffuse slow background and waves (21%), and alpha coma (7%). These severe diffuse EEG abnormalities are consistent with marked diffuse cerebral dysfunction. The reported exact temporal association between these EEG abnormalities and the myoclonus is both variable and imprecise. Even generalized epileptiform discharges were variably reported as being not correlated with the myoclonus, or correlated inconsistently without a fixed interval.
| Reference                | Findings                                                                                                                                       | Outcome                                                                 |
|--------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Baldy-Moulinier et al.   | EEG demonstrated bilaterally synchronous spikes and wave.                                                                                 | Patient survived and developed short term memory loss.                |
| Madison and Niedermeyer  | Case 1: continuous generalized synchronous multiple spikes and spike wave like discharges associated with myoclonic jerks.                | Cases 1 and 2 survived while the other three patients died.             |
|                          | Case 2: continuous rhythm 2 to 3 per second with a definite spike component.                                                                   |                                                                        |
|                          | Case 3: generalized synchronous sharp waves of high voltage and a small number associated with myoclonus.                                 |                                                                        |
|                          | Case 4: excessive diffuse slow activity.                                                                                                      |                                                                        |
|                          | Case 5: high voltage delta activity; no spikes were noticed.                                                                                        |                                                                        |
| Van Woert et al.         | EEG: diffuse slowing and occasional theta activity.                                                                                           | This patient survived and went on to develop LAS.                      |
| Wolf                     | Myoclonus was associated with EEG bursts.                                                                                                      | None of the patient survived post-anoxic myoclonus.                    |
| Niedermeyer et al.       | Spike activity on EEG seen with myoclonus.                                                                                                     | Patient did not regain consciousness and died.                         |
| Jumao-as et al.          | EEG performed in 15 patients with anoxic encephalopathy showed burst suppression and generalized periodic complexes as the most common pattern. | None of the patients regained consciousness and all died.             |
| Young et al.             | EEG performed in 6 patients with generalized myoclonus after CPR: burst suppression and alpha coma was commonly seen.                           | None of the patients with generalized myoclonus after CPR regained consciousness. |
| Harper et al.            | EEG showed occasional bursts of activity at 7–11 Hz.                                                                                           | Patient survived and developed LAS.                                   |
| Wijdicks et al.          | Common EEG pattern seen in cases of generalized myoclonus after CPR included burst suppression, polyspiked waves, and alpha coma.             | None of the patients with generalized myoclonus after CPR regained consciousness. |
| Wijdicks                 | EEG: burst suppression pattern in 2 patients after hypoxia.                                                                                     | Both patients died.                                                   |
| Zivkovic and Brenner     | No changes in EEG with myoclonus. Tactile stimulation led to generalized spike and wave discharges and generalized myoclonus.               | Patient did not regain consciousness and died.                         |
| Hui et al.               | EEG was performed in 10 patients who developed generalized myoclonus after anoxia; 6 patients had generalized polyspikes related to myoclonus while other 4 had low voltage diffuse activity. | 16 out of 18 patients with generalized myoclonus died while 1 remained in a persistent vegetative state and another one developed LAS. |
| Thömke et al.            | Different patterns of EEG were described: burst suppression, continuous generalized epileptiform discharges, and alpha coma.                   | 45 patients with generalized myoclonus after CPR died while 5 remained in a permanent vegetative state. |
| Fernández-Torre et al.   | EEG showed burst suppression pattern. Generalized spike and wave discharges were precipitated with touch.                                      | Patient did not regain consciousness and died.                         |
| Reference                  | Findings                                                                 | Outcome                                      |
|---------------------------|---------------------------------------------------------------------------|----------------------------------------------|
| Kakisaka et al.\(^{26}\)  | EEG: burst suppression pattern. EMG: agonist and antagonist muscle contract simultaneously. | Patient survived with significant disabilities. |
| Fernández-Torre et al.\(^{8}\) | EEG: periodic, regular, generalized burst of slow waves intermixed with prominent spikes, polyspikes, and sharp waves. This pattern was accompanied with eye opening movements. | Patient did not regain consciousness and died. |
| Legriel et al.\(^{10}\)   | EEG: artifacts associated with jerks.                                     | Patient did not regain consciousness and died. |
| Arpesella et al.\(^{56}\) | EEG: continuous spikes, polyspikes, and slow wave diffuse activity.        | Patient survived and developed LAS.          |
| English et al.\(^{71}\)    | EEG: frequent myoclonic polyspikes were observed.                         | Patient developed LAS but eventually died of pneumonia. |
| Datta et al.\(^{29}\)      | EEG: continuous generalized sharp and slow epileptiform activity disrupted by bursts of generalized polyspikes. This was not associated with myoclonus. | Patient developed LAS but died later due to hemoptysis. |
| Rosetti et al.\(^{17}\)    | EEG in two patients with myoclonus showed bilateral, repetitive, and diffuse sharp waves; third patient: demonstrated sharp, spike waves with stimulus induced rhythmic, periodic, or ictal discharges. All three patients had preserved N20 on SEP. Five patients with axial myoclonus without corresponding EEG changes died. 23 patients with myoclonus demonstrated ictal EEG. Only one patient survived out of 23. | 2 out of 3 patients who survived cardiac arrest went on to develop LAS. They were treated with therapeutic hypothermia. |
| Thömke et al.\(^{31}\)     | EEG: burst suppression pattern in 39 out of 60 patients and continuous generalized epileptiform discharges in the rest. | 59 patients died and one survived in a persistent vegetative state. |
| Rajamani et al.\(^{13}\)   | EEG: generalized periodic discharges with no perceptible background rhythm. | Patient did not regain consciousness and died. |
| Lee and Lee\(^{41}\)       | EEG: complex spike waves bifrontally.                                     | Patient developed LAS.                       |
| Bouwes et al.\(^{25}\)     | 3 out of 51 SEPs were giant; EEG: epileptiform activity (33%); status epilepticus (22%); generalized periodic discharges (25%); burst suppression (5%) | Good outcome was observed in 12% of the patients with acute PHM. Only one patient with status myoclonus survived and made a good recovery. |
| Lucas et al.\(^{21}\)      | Case 1: EEG: diffusely slow background; Case 2: EEG: burst suppression pattern followed by intermittent epileptiform activity; Case 3: EEG: slow and disorganized background rhythm. | All three patients survived following treatment with therapeutic hypothermia (one patient later died of septic shock). |
| Legriel et al.\(^{72}\)    | EEG: burst suppression.                                                    | Patient did not regain consciousness and died. |
| Fernández-Torre et al.\(^{73}\) | EEG: burst suppression.                                                   | Patient did not regain consciousness and died. |
| Shin et al.\(^{74}\)       | EEG: cyclic epileptiform waves.                                           | Patient survived and developed LAS.          |
| Mader et al.\(^{75}\)      | EEG: spike and wave activity.                                            | Patient did not regain consciousness and died. |
| Reference         | Findings                                                                                                                                                                                                 | Outcome                                                                                                                                                                                                 |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Accardo et al.    | Unreactive EEG with diffuse epileptiform discharges associated with continuous generalized multifocal myoclonus.                                                                                          | Patient developed LAS.                                                                                                                                                                                 |
| Tsai et al.       | EEG showed diffuse cortical dysfunction                                                                                                                                                                   | Myoclonus was observed after the discontinuation of muscle relaxant which was done for therapeutic hypothermia. Patient regained consciousness after 15th day of cardiac arrest. |
| van Zijl et al.   | EEG in generalized myoclonus group revealed status epilepticus (54%), diffuse slowing (17%), and burst suppression (11%). Multifocal myoclonus group had diffuse slowing (52%), low voltage (13%), and status epilepticus (13%). | Only 1 patient out of 17 with generalized myoclonus survived. 3 patients out of 43 with PHM developed LAS. 34 patients out of 43 with PHM died.                                                                |
| Seder et al.      | EEG: 27% electrographic status epilepticus; 55% epileptiform activity (electrographic seizure or periodic epileptiform discharges)                                                                         | Good outcome in patients when myoclonus was not associated with epileptiform activity on EEG.                                                                                                           |
| Dericioglu et al. | EEG: generalized high-amplitude, spike and sharp wave complexes. Around 50 hours after arrest, EEG showed bilateral independent discharges.                                                               | Patient did not regain consciousness and died.                                                                                                                                                           |
| Sanna et al.      | Alpha coma pattern was seen on EEG.                                                                                                                                                                       | progressed to develop LAS.                                                                                                                                                                              |
| Walsh BH et al.   | EEG showed suppressed background with intermittent rhythmic pattern which was later observed to be an artifact.                                                                                           | Patient did not regain consciousness and died.                                                                                                                                                           |

Abbreviations: CPR, Cardiopulmonary Resuscitation; EEG, Electroencephalography; LAS, Lance–Adams Syndrome; PHM, Post-hypoxic Myoclonus; SEP, Somatosensory Evoked Potential.
between the EEG change/discharge and myoclonus. Thus, the important unanswered question for the reported EEG discharge abnormalities is whether they are epiphenomena, interictal, or direct ictal discharges responsible for the myoclonus jerk. It is possible that different cases have different pathophysiology. In one study, only three of 51 SEP had enlarged cortical components.25 A single report with EMG mentioned co-contraction between muscles but no recruitment order or duration was given.26 Without more documented surface EMG studies of the generalized jerk, it is difficult to assign an exact relationship between the EEG discharges and the jerk as well as to define the myoclonus source in general.

The exact neuronal damage and pathophysiology that gives origin to acute PHM is not clear. Histopathological studies in patients with post-hypoxic myoclonus have demonstrated neuronal loss in cortical laminae, loss of Purkinje cells, and ischemic damage in the hippocampus, thalamus, and brainstem.5,15 Animal models of PHM have shown neuronal injury in the cerebral cortex, the hippocampus, the Purkinje cell layer of the cerebellum, and the reticular thalamic nucleus.27 It is possible that acute PHM can arise from the cortex or a subcortical structure.26 Indeed, it is hard to determine the origin of myoclonus on the basis of clinical judgment since multiple pathophysiology mechanisms may produce similar clinical phenomena.12 Hallett et al. in 197728 described the origin of myoclonus after post-hypoxic injury in the reticular formation of the medulla oblongata and called this “reticular reflex myoclonus.” This type of myoclonus is stimulus sensitive and present at rest; the proximal muscles are more involved than the distal, flexor more than extensor, and it is generalized with initial activation of the muscles innervated by lower brainstem nuclei followed by rostral and caudal recruitment spread. EMG discharges in the affected muscles are brief (10–30 ms) and EEG discharges (spike and slow waves) are variably associated with myoclonus but not time locked to it. For some of these jerks, EEG changes are present, but clearly after the initial EMG discharges. Interestingly, this described “reticular reflex myoclonus” may be chronic in conscious patients, but the jerks themselves resemble acute generalized PHM in clinical appearance. As a result, some have thought the physiology of reticular reflex myoclonus to mimic the generalized myoclonus in acute PHM while in coma. Although a logical possibility, EMG studies are lacking to document that such simultaneous rostral and caudal recruitment is common in acute generalized PHM during coma. Injury to the cortex after hypoxia is another possible cause of brainstem origin for acute PHM in which the cortex is unable to generate inhibitory activity on spontaneous brainstem discharges. In contrast to generalized myoclonus, multifocal acute PHM is more confidently believed to arise from the cortex.6,7,29 Recent studies have demonstrated that acute generalized PHM can arise from the cortex as well, which is not in agreement with the previous studies.12,25 Acute PHM can also be associated with seizures, and it is possible that a generalized ictal discharge produces a generalized jerk, at least in some of these cases.3,14 This may be the case particularly when generalized epileptiform discharges are periodic and the generalized myoclonus is also periodic. In another possible cortical mechanism, a focal cortical discharge spreads ipsilateral and contralateral via the corpus callosum, effectively producing bilateral and generalized motor cortex discharge. It is possible that variable cortical and subcortical injuries after hypoxic injury may lead to the mixed and varying clinical findings of this myoclonus.30

Figure 1. Neurophysiological findings in acute PHM. More than one pattern of electroencephalography was seen in the same patient during the course of myoclonus. Burst suppression was the most common pattern while alpha coma was the least common pattern observed. The highest rate of survival was seen in the diffuse slowing group and the lowest rate was seen in the spike-wave group. Multiple studies were commonly performed in the same patient.
There are no published guidelines for the treatment of acute PHM, and reported treatment is mostly anecdotal, so caution and skepticism should be exercised. If epileptiform discharges are present, initial treatment should consider antiepileptic drugs such as phenytoin, phenobarbitone, and benzodiazepines. If these efforts are ineffective in the treatment of acute PHM, anesthesia agents should be considered. Infusion of propofol has been reported to benefit myoclonus arising after acute hypoxia. However, there are also case reports where propofol has been reported to cause myoclonus in healthy subjects but is short lasting and self-limiting.

**Chronic post-hypoxic myoclonus: Lance–Adams syndrome**

Our search found 77 articles with chronic post-hypoxic cases (LAS). All but one of the articles (where 14 patients with LAS were studied) represented case reports or case series. Several case reports have been published since the original description of this syndrome in 1963. Two major reviews of this syndrome were published in 1986 and 2000. The major cause of hypoxia was respiratory arrest followed by anesthesia and surgical accidents. Few cases of LAS have been reported after cardiac arrest, drug intoxication, and asthma attack. Commonly, the myoclonus appears days or weeks after the hypoxic episode when consciousness is regained. It is characteristic that the myoclonus is exacerbated during muscle activation (“action myoclonus”) or even intention (“intention myoclonus”). This is the most common clinical feature described and it significantly interferes with daily tasks and impairs the quality of life. In some cases, myoclonus was triggered by sensory stimuli such as touch or sound (reflex myoclonus), or with anxiety. Negative myoclonus can also be present in the lower extremities, leading to falls from lapses in postural tone. Other features such as dysarthria, dysphagia, seizures, cognitive deficits, and gait dysfunction were commonly seen in these patients. Dysarthria and ataxia may improve with time but action myoclonus persists for life, except for rare cases where complete resolution of the myoclonus has been described. Some case reports do mention the presence of seizures in the comatose stage acutely after the hypoxic episode, and acute PHM was present in a higher proportion of patients who went on to develop LAS. Currently, there is no scoring system to predict the patients who do survive anoxic brain injury and eventually develop LAS. The duration of coma and severity of anoxic injury is highly variable in the reported cases of LAS, which makes it difficult to draw any conclusion. However, one study suggested that patients in a relatively milder cerebral performance category are the ones who develop LAS.

It is not properly understood which neurons are critically injured in order to generate the myoclonus in LAS. Initially, serotonergic mechanisms were implicated in the development of LAS because of a partial response to serotonergic treatment and low cerebrospinal levels of serotonin metabolites. An autopsy of a LAS case showed astrocytic prominence in the midbrain periaqueductal gray, supratrochlear nucleus, the lateral subnucleus of the mesencephalic gray matter, and the cuneiform and subcuneiform nuclei. Other cases have shown neuronal loss in the thalamus, striatum, mammillary bodies, and brainstem raphe nuclei. The differences in pathology could be due to the etiology of hypoxia or duration of the syndrome.

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**Figure 2. Neurophysiological findings in CHRONIC PHM (LAS).** Electroencephalography is the most common neurophysiological study followed by jerk-locked back averaging in chronic post-hypoxic myoclonus. An overwhelming majority of myoclonus in chronic PHM was found to be of cortical origin with jerk-locked back averaging. Multiple studies were commonly performed in the same patient.
diffuse damage, but the key areas that must be involved for the LAS remain elusive.

Movement neurophysiology studies have been very useful in determining the generator of LAS myoclonus. Seventy-nine cases in the 51 articles that reported neurophysiological findings with LAS are listed in Table 2. The neurophysiological findings reported in chronic PHM are summarized in Figure 2. The number of articles where various neurophysiological techniques have been applied to LAS has been described is as follows: 46 EEG, 15 surface EMG, 14 SEPs, 11 jerk-locked back-averaging, and one with the long latency reflex. EEG was described as spike-wave or polyspike activity in 29 cases and having slower EEG frequency waves in 14 cases. The result from back-averaging myoclonus was concluded to be focal cortical origin in seven articles (23 cases). The action myoclonus in LAS is thought to be the classic example of cortical origin myoclonus. In some cases, an EEG spike, focal or more widespread, can be appreciated before the myoclonus. For most cases, using back-averaging of the EEG by jerk-locking or EMG discharges reveals a relatively focal EEG discharge over the appropriate sensorimotor cortical area. Characteristically, the EMG discharge is brief during multifocal myoclonus, lasting 50–100 ms or less with nearly synchronous EMG discharges in agonist, antagonists, and contiguous muscle segments. An enlarged cortical SEP was observed in many but not all cases. Enhance long-latency EMG reflexes, consistent with latency for a transcortical loop, was demonstrated and may correlate with reflex-induced myoclonus on examination ("cortical reflex myoclonus"). Broader muscle activation may occur, including bilateral jerks, via intra-hemispheric and corpus callosum spread. Other EEG findings such as interictal epileptiform discharges and slower EEG frequencies are common. Intercital epileptiform discharges may correlate with the presence of clinical seizures. Although reticular reflex myoclonus was initially described in a case of chronic PHM, it is rarely encountered in clinical practice.

Imaging studies were performed either very early after hypoxia or late in the disease course. A report published in 2013 mentioned early and transient restricted diffusion in cerebellum and thalami that disappeared when magnetic resonance imaging (MRI) was repeated 20 days after cardiac arrest. Another case showed transient abnormalities in lenticular nuclei and periventricular areas. A functional imaging study of LAS demonstrated increased glucose metabolism in the ventrolateral thalamus and pontine tegmentum. A resting state functional MRI (rs-fMRI) showed increased functional connectivity between different cortical areas in a patient with LAS. Brain single photon emission computed tomography has shown decreased perfusion in the basal ganglia, frontal lobe, parietal lobe, and the left temporal lobe in LAS cases. In another case of LAS, [18F]-fludeoxyglucose positron emission tomographic scan showed a decrease in glucose metabolism in the bilateral frontal lobes, and in the same patient magnetic resonance spectroscopy displayed neuronal loss in the hippocampus. Similar to the pathology studies, characteristic structural or functional imaging has yet to be defined.

Multiple large controlled treatment trials are not available for guiding treatment in LAS, so a cautious approach should be emphasized. Older treatment studies have demonstrated the beneficial effect of L-5-hydroxytryptophan (L-5-HTP), 5-HTP is the immediate precursor of serotonin and improvement in myoclonus following the administration of L-5-HTP may be alleviating the deficiency of serotonin. The side effects of L-5-HTP such as nausea, vomiting, and diarrhea may be lessened by combining with carbidopa (inhibitor of aromatic L-amino acid decarboxylase). 5-HIAA (5-hydroxyindoleacetic acid), a metabolite of serotonin, has been shown to rise in the cerebrospinal fluid (CSF) after the administration of L-5-HTP. Some patients did not improve following the administration of L-5-HTP, which suggests that complex mechanisms may be involved in the generation of myoclonus other than serotonin deficiency. Indeed, in a report published in 1988, the CSF 5-HIAA level was increased at baseline and the administration of L-5-HTP made the myoclonus worse. The administration of methysergide (a serotonin receptor antagonist) improved the myoclonus and led to a decrease in the level of CSF 5-HIAA in a few cases. However, the majority of the reports have mentioned that methysergide makes the myoclonus worse.

Owing to the side effects of L-5-HTP and concerns about methysergide, these treatments are now uncommonly used for LAS. In the animal model of myoclonus, improvement was seen with valproate, clonazepam, 5-HTP, lamotrigine, levetiracetam, and riluzole. Since the myoclonus is of cortical origin most commonly, such a treatment approach is often used. Therapy with diazepam has not been uniformly successful in controlling the myoclonus seen in LAS. Clonazepam, another benzodiazepine, was first shown to be effective in the treatment of LAS in 1976. Doses of clonazepam as high as 18 mg per day have been used in severe cases of LAS. The possible mechanism of action in the case of clonazepam is facilitation of GABAergic transmission and a decrease in 5-hydroxytryptophan utilization in the brain. The reason for the potent antmyoclonic action of clonazepam compared with other benzodiazepines is still unclear. Piracetam, one of the nootropic agents, has shown some benefit in the improvement of myoclonus, but this drug is not licensed in the United States. Levetiracetam, which is chemically related to piracetam, has shown marked improvement in myoclonus associated with LAS. For the treatment of refractory cases of LAS, deep brain stimulation surgery has been performed with some initial encouraging results, but only in a few cases and it is still experimental at this time. In a case of perinatal hypoxia, the target of stimulation was the thalamus but in the other two cases the stimulation target was the globus pallidus internus. Further work on deep brain stimulation
| Reference | EEG | EMG | Jerk-locked Back-averaging | Long Latency Reflex | SEP |
|-----------|-----|-----|---------------------------|-------------------|-----|
| Lance and Adams<sup>2</sup> | Case 1: spike discharges at paracentral electrode. | Spike was usually recorded in all muscles of the limb; contraction was stronger in flexors. | Myoclonic jerks followed shortly after spikes; duration of negative cortical spike varied from 15–35 ms and followed by positive deflection of 10–15 ms. | NA | NA |
| Erbslo¨h and Prue¨ll<sup>79</sup> | 2–4 c/sec spike and wave; polyspike and wave synchronous with the myoclonus. | NA | After a latency of 20–50 ms following the cortical spikes myoclonus was observed. | NA | NA |
| Hirose et al.<sup>80</sup> | Bitemporal independent random low amplitude delta slowing. No cortical spike potentials were observed. | NA | NA | NA | NA |
| Tassinari et al.<sup>31</sup> | Well-preserved background activity with rare bursts of low voltage sharp theta activity. During REM sleep, typical long lasting bursts of fast spikes over the midline and frontocentral regions. | NA | NA | NA | NA |
| Van Woert et al.<sup>62</sup> | Case 1: moderate generalized slow activity with occasional sharp waves. | NA | NA | NA | NA |
| Goldberb and Dorman<sup>48</sup> | Case 1: mild slowing. Case 2: focal spikes. Case 3: normal. | NA | NA | NA | NA |
| De Léan et al.<sup>13</sup> | Case 1: Muscle artifact; no spike activity observed. Case 2: slow activity over the left hemisphere; no spike activity. | NA | NA | NA | NA |
| Hallett et al.<sup>28</sup> | Slow and fast activity over both hemispheres and very frequent spikes followed by slow waves. | The duration of EMG was 10-30 msec. Cranial nerve nuclei were activated in ascending order and arm muscles before the leg. | EEG spikes were not time locked to EMG discharges. | NA | Normal. |
| Reference            | EEG                                                                 | EMG                                                                 | Jerk-locked Back-averaging | Long Latency Reflex | SEP        |
|----------------------|----------------------------------------------------------------------|----------------------------------------------------------------------|----------------------------|---------------------|------------|
| Carroll and Walsh    | Central intermittent single and short duration multiple spike and slow wave complexes. Background activity was 6–7 Hz theta activity. Some discharges were associated with myoclonus. | NA                                                                  | NA                         | NA                  | NA         |
| Hallett et al.       | Diffusely slow with mixed sharp waves.                               | Simple waveform lasting 10 to 30 msec. Cranial muscles activated before the arm and arm muscles before the leg. | An EEG negative transient preceded and was time locked to the myoclonus. | NA                  | Giant SEPs |
| Fahn                | Case 1: generalized spike and slow wave complexes that were maximum parasagittally. Case 2: generalized spike and slow wave complexes that were maximal in frontocentral region. Case 3: fast activity in the frontocentral region. | Case 1: bilaterally symmetrical motor unit discharges that were synchronous in all extremities. Case 2: synchronous contraction in all muscle groups tested. There was no correlation between myoclonic jerks and epileptiform discharges. | NA                         | NA                  | Case 1: normal Case 2: normal Case 3: high amplitude waves |
| DeLisa et al.        | Normal                                                               | NA                                                                  | NA                         | NA                  | NA         |
| Bruni et al.         | Frequent bisynchronous spike and polyspike and wave localized to centroparietal region. No relationship was observed between EEG and myoclonus. | NA                                                                  | NA                         | NA                  | NA         |
| Rollinson and Gilligan | Normal                                                             | NA                                                                  | NA                         | NA                  | NA         |
| Coletti et al.       | Paroxysms of symmetrical sharp waves of large amplitude and bursts of polyspike and spike-wave over the central regions. Demonstrated simultaneous involvement of agonist and antagonist muscles. | Simultaneous EEG-EMG recording did not demonstrate correlation between myoclonus and EEG. | NA                         | NA                  | NA         |
| Kelly et al.         | Normal                                                               | NA                                                                  | NA                         | Normal              | Normal     |
| Reference | EEG | EMG | Jerk-locked Back-averaging | Long Latency Reflex | SEP |
|-----------|-----|-----|--------------------------|-------------------|-----|
| Sotaniemi<sup>89</sup> | Symmetric slowing and intermittent delta activity. | NA | NA | NA | NA |
| Magnussen et al.<sup>90</sup> | Case 1: normal when myoclonus appears. Case 2: 4–6 Hz activity without changes related to the myoclonus. | NA | NA | NA | NA |
| Obeso et al.<sup>91</sup> | Excess of generalized theta activity. | Duration of EMG discharge was 60 to 120 msec. | EEG potential was not time locked to the jerk. | NA | Not enlarged. |
| Chee and Poh<sup>92</sup> | 5–6 cps theta activity. No epileptiform activity detected. | NA | NA | NA | NA |
| Fahn<sup>33</sup> | Case 5: EEG showed spontaneous paroxysmal crises with spike activity associated with myoclonus. Case 2: EEG showed bilateral delta waves and no spike activity. Case 3: EEG did not show spike associated with myoclonus. Case 4: EEG showed slow waves of 4–5 Hz with intermittent paroxysmal potentials. | Case 1: EMG shows synchronous and asynchronous firing of leg flexors and extensors. | Case 5: jerk-locked averaging failed to show cortical spikes. | NA | Case 5: normal. Case 6: normal. |
| Hauw et al.<sup>36</sup> | Case 1: EEG showed spontaneous paroxysmal crises with spike activity associated with myoclonus. | NA | NA | NA | NA |
| Kim et al.<sup>53</sup> | Slow theta to delta waves were seen in both hemispheres. | NA | NA | NA | Normal. |
| Giménez-Roldán et al.<sup>45</sup> | 4–6 Hz bitemporal runs; no activity with myoclonus observed. | NA | NA | NA | NA |
| Witte et al.<sup>94</sup> | Spike activity at the vertex when patient performed any movement. | Simultaneous EEG–EMG showed that spikes were present before any myoclonic movement was observed. | NA | NA | Normal. |
| Reference                        | EEG          | EMG                        | Jerk-locked Back-averaging | Long Latency Reflex | SEP            |
|---------------------------------|--------------|----------------------------|----------------------------|---------------------|----------------|
| Obeso et al. 95                 | NA           | EMG discharges were brief (less than 50 ms). | NA                        | NA                  | Enlarged       |
| Brown et al. 30                 | Generalized and polyphasic spikes followed by slow wave. The spikes were usually associated with myoclonus. | EMG activity lasting 25–100 ms. | Positive peak preceded the jerk by 10 ms. | NA      | Disorganized and of small amplitude. |
| Rizzi and Karetzky 96           | Normal       | NA                        | NA                        | NA                  | NA             |
| Wicklein and Schwendemann 97    | Spike and wave activity variably related to the myoclonus. | NA                        | NA                        | NA                  | NA             |
| Yamaoka et al. 98               | Case 1: spike discharge. Case 2: alpha and theta waves and no spike discharge was seen. | NA                        | NA                        | NA                  | NA             |
| Werhahn et al. 59               | 7 out of 14 patients with LAS had abnormal EEG. These included: bilateral spikes, sharp waves, polyspike wave complexes sometimes associated with myoclonus. | NA                        | All patients except one had a time-locked cortical correlate preceding myoclonus. | NA      | 2 out of 14 patients with LAS had pathologically enlarged cortical SEPs. One patient had normal SEPs. |
| Lance and Adams, 2001 100       | Simultaneous EEG–EMG recording showed spike discharges preceding myoclonus by 7 ms for occipital muscles and 32 ms for quadriceps. | NA                        | NA                        | NA                  | NA             |
| Krauss et al. 50                | Case 1: several temporal-central spikes. Case 2: generalized slowing but no epileptiform discharges. | NA                        | NA                        | NA                  | NA             |
| Frucht et al. 38                | NA           | NA                        | NA                        | NA                  | NA             |
| Polesin and Stern 57            | Spike and polyspike discharges over the vertex region which was consistent with her myoclonic jerks. | NA                        | NA                        | NA                  | NA             |
| Reference            | EEG                                      | EMG | Jerk-locked Back-averaging | Long Latency Reflex | SEP |
|----------------------|------------------------------------------|-----|----------------------------|---------------------|-----|
| Zhang et al.         | Case 1: low amplitude alpha waves, diffuse delta activity, and sharp and slow waves at night. No epileptiform discharge during myoclonus. Case 2: low amplitude theta waves mixed with faster waves; no epileptiform discharge during myoclonus. | NA  | NA                         | NA                  | NA  |
| Datta et al.         | Sporadic generalized epileptiform discharges not correlated with myoclonic jerks. | NA  | NA                         | NA                  | NA  |
| ArpeseLLa et al.     | Diffuse alpha activity mixed with theta. | NA  | NA                         | NA                  | NA  |
| Yamada et al.        | No epileptiform discharges. Brief generalized bursts lasting 20–30 ms. | NA  | EEG event 26 ms prior to the myoclonus. | NA                  | NA  |
| Huang et al.         | NA                                       | Short duration (<30 ms) myoclonic bursts. | EEG–EMG simultaneous recording revealed a time locked cortical discharge preceding myoclonus and myoclonus without a correlated EEG. | NA  | NA  |
| González de la Aleja et al. | Generalized spike and slow wave complexes with mild background slowing. | EEG–EMG simultaneous recording showed generalized spike and polyspike-wave discharges associated with myoclonus. | EEG–EMG simultaneous recording showed generalized spike and polyspike-wave discharges associated with myoclonus. | NA  | NA  |
| Accardo et al.       | Normal background with isolated brief polyspike discharges associated with myoclonic jerk. | NA  | NA                         | NA                  | NA  |
| Cho et al.           | Normal                                   | NA  | NA                         | NA                  | NA  |
| Ferlazzo et al.      | NA                                       | EEG–EMG simultaneous recording showed generalized spike and polyspike-wave discharges associated with myoclonus. | EEG–EMG simultaneous recording showed generalized spike and polyspike-wave discharges associated with myoclonus. | NA  | NA  |
| Ilik et al.          | Frequent myoclonic polyspikes.           | NA  | NA                         | NA                  | NA  |
| Reference       | EEG                                              | EMG | Jerk-locked Back-averaging | Long Latency Reflex | SEP |
|-----------------|--------------------------------------------------|-----|----------------------------|---------------------|-----|
| Budhram et al.  | Case 1: generalized spike and polyspike wave discharges which correlated with myoclonic jerks. Case 2: no epileptiform activity was observed. | NA  | NA                         | NA                  | NA  |
| Božić et al.    | Spikes and polyspikes on slow wave background activity. The EEG spikes were highly frequent and generalized. Myoclonus and EEG abnormalities were not linked to each other. | NA  | NA                         | NA                  | Normal. |
| Asahi et al.    | NA                                               | Showed a cortical myoclonus pattern. | NA                  | NA                  | Normal. |
| Park et al.     | Frequent bilateral central or hemispheric spike or poly-spike discharges. | NA  | NA                         | NA                  | NA  |
| Sanna et al.    | Spike and slow wave synchronous with myoclonus.  | NA  | NA                         | NA                  | NA  |

Abbreviations: EEG, Electroencephalography; EMG, electromyography; LAS, Lance–Adams Syndrome; NA, Not Applicable; SEP, Somatosensory Evoked Potential.
surgery will hopefully confirm effectiveness and clarify the preferred site of stimulation. Intrathecal baclofen therapy has also been shown to improve myoclonus in a patient refractory to multiple medications. Based on a review in 2000, the following drugs were not found to be helpful in treating myoclonus: amantadine, phenytoin, tetrabenazine, nitrazepam, phenobarbitone, primidone, norriptyline, and vaso-pressure. Some reports have mentioned the usefulness of lacosamide,56 sodium oxybate,56 zonisamide,57 and agomelatine.58

**Conclusion**

There seem to be two fairly distinct clinical syndromes for PHM, acute and chronic. Either or both may occur in the same patient. Most commonly, acute PHM occurs within hours of the hypoxia while the patient is unconscious, has a generalized/bilateral distribution, and commonly demonstrates severe generalized EEG abnormalities including epileptiform discharges. Studies of acute PHM with neurophysiological studies that include EMG are needed to clarify its possible and variable sources. Acute PHM may arise from the brainstem, represent seizures, or another phenomenon. Benzodiazepines or anesthetic agents are the most effective treatments reported anecdotally. Chronic PHM, or LAS, develops remote from the hypoxia when the patient has regained consciousness, and presents as multifocal action myoclonus. Neurophysiology studies demonstrate sensorimotor cortical activation through pre-myoclonus epileptiform discharges or back-averaged EEG transients time-locked to the myoclonus. Enlarged cortical SEPs and enhanced long-latency reflexes may be present. Since a cortical source for LAS action myoclonus is firmly documented in the literature, we suggest using a cortical source approach for treatment. Although little controlled evidence is available, levetiracetam, clonazepam, or valproic acid, either alone or in combination is reasonable but not a proven treatment approach for LAS, consistent with a cortical source.59 Deep brain stimulation surgery is a promising treatment for LAS which should be studied further.

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