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Case Report

Post hypoxic myoclonus: A tale of two minds

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ABSTRACT

Post hypoxic myoclonus (PHM) is considered a poor prognostic sign and may influence decisions regarding withdrawal of treatment. PHM is generally categorized in literature as either acute or chronic (also commonly referred to as Lance-Adams Syndrome) based on the onset of myoclonus. However, it may be more accurate to differentiate between the various presentations of PHM based on the clinical characteristics and electroencephalogram (EEG) findings for prognostication. Here, we describe a case of a 33-year-old female who presented after a cardiopulmonary arrest. MRI of the brain and cervical spine on admission were unremarkable. Twelve hours later, she developed generalized, stimulus-sensitive myoclonus suggestive of acute PHM. Various medications were trialed, and her symptoms eventually improved on clonazepam. On day 14, she started having resting and intention myoclonus, and dysarthria, consistent with LAS. Several adjustments were again made to her regimen, and she was eventually switched from clonazepam to baclofen which improved her resting myoclonus. This case highlights that PHM can present differently and have a markedly different outcome. It is important to develop a better understanding of the various types of PHM so as to avoid premature withdrawal of care.

Introduction

Post hypoxic myoclonus (PHM) is generally categorized in literature as either acute or chronic based on the onset of myoclonus. However, it is also important to differentiate between the various presentations of PHM based on their clinical characteristics and electroencephalogram (EEG) findings as this may have implications on the overall prognosis [1].

Acute PHM typically presents as multifocal or generalized myoclonus within 12–48 h of hypoxic brain injury. It typically presents before a patient has regained consciousness and is usually transient, lasting only a few days [2]. Prognosis is variable: Patients with acute PHM might die, progress to a chronic vegetative state, achieve complete remission in symptoms, or go on to develop chronic PHM [3].

Chronic PHM, commonly referred to as Lance-Adams Syndrome (LAS), generally presents as a multifocal intention or action myoclonus along with generalized, startle-sensitive jerks that appear days to weeks after the resolution of coma [4]. Patients may also develop myoclonus affecting facial muscles causing dysphagia and dysarthria. LAS carries a much more favorable prognosis, with a higher likelihood of patients regaining consciousness, though that can take up to several weeks [5]. Despite the potential for cognitive recovery, patients might continue to have significant functional impairment, requiring long-term treatment [6].

There is limited data about the optimal management of PHM. Most of the evidence available regarding treatment strategies is anecdotal and does not differentiate between the different subcategories of PHM. Here we describe a case of PHM, with emphasis on the distinguishing features of acute PHM versus LAS and its impact on the pharmacologic management and overall prognosis of PHM.

Case

A 33-year-old female with a history of asthma presented after a witnessed out-of-hospital respiratory arrest leading to cardiac arrest. She had reportedly been experiencing shortness of breath and wheezing prior to her arrest. Resuscitative efforts were begun by bystanders and subsequently taken over by emergency medical services. The patient was intubated in the field and received intramuscular naloxone. She attained return of spontaneous circulation after about 15 min of cardiopulmonary resuscitation. Upon presentation to the hospital, the patient was still comatose, but her brainstem reflexes were intact. She was noted to have an esophageal intubation and was subsequently re-intubated. On secondary survey, she was found to have a bag of heroin in her sock. Toxicology

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screen was positive for fentanyl. Magnetic resonance imaging (MRI) of the brain was obtained at the time of admission and did not show any findings concerning for anoxic brain injury.

Within 12 hours of resuscitation, while she was still comatose, the patient developed generalized, stimulus-sensitive myoclonic jerks involving her arms, legs, and trunk with relative sparing of her face. Her diffuse, violent jerks led her to develop rhabdomyolysis necessitating propofol infusion for symptom control and precluding her from being weaned off sedation for an accurate neurological assessment. EEG obtained on day 3 of hospitalization, while the patient was still sedated, showed diffuse anteriorly prominent alpha and beta activity and occasional periods of diffuse delta slow-waves and diffuse voltage suppression and lack of any cerebral reactivity to external stimuli. A number of diffusely distributed bilaterally synchronous spike and wave epileptiform discharges were also noted. Given her overall picture with relative paucity of findings on MRI of the brain despite significant clinical myoclonus and findings on EEG, an MRI of the cervical spine was obtained but showed no notable findings consistent with anoxic injury.

The patient was started on ketamine infusion which, in addition to propofol, significantly improved her myoclonus. She was also started on valproate (1 g three times a day) and levetiracetam (2 g twice daily). By day 4–5 of her hospital course, the patient regained consciousness and was noted to have some improvement in her motor activity, though she continued to have significant stimulus-sensitive myoclonus. The patient was subsequently weaned off propofol and ketamine infusions. She was switched to clonazepam (2 mg three times daily) which, in addition to valproate and levetiracetam, significantly improved her symptoms, though she never achieved complete remission in her symptoms. Her neurological function gradually improved to the point where she was able to follow simple commands. Her sedation was weaned and the patient was subsequently extubated and transferred out of the ICU on day 11 of her hospitalization.

The patient remained on clonazepam and levetiracetam. Valproate was discontinued two weeks into her hospital course due to concern for drug-induced transaminitis. She was switched to zonisamide (100 mg three times a day) and remained on this combination regimen for the next two weeks. Approximately one month into the patient's hospital course, she started to exhibit significant resting and intention myoclonus as well as dysarthria, not responding to the current treatment. She underwent another video EEG and was noted to have recurrent episodes of jerking, of which some, but not all, were associated with underlying poly-spike discharges. The clinical impression of the neurology team was that the episodes not associated with poly-spike discharges could represent some component of brainstem or spinal myoclonus. The clinical team had a lower suspicion for functional myoclonus given the patient's overall clinical picture, though it could not be fully excluded based on scalp EEG. At this point, clonazepam did not seem to be significantly helpful in achieving symptom control and it was subsequently tapered off. Instead, the patient was treated with baclofen (20 mg every 6 hours) with significant improvement in her resting myoclonus, though she continued to have intention myoclonus. She was eventually discharged to a skilled nursing facility for further rehabilitation. She was seen again a month after her discharge for an unrelated complaint, and while she had preserved cognition and sensorimotor function, she continued to have significant, debilitating intention myoclonus.

Discussion

Myoclonus is a common manifestation of neurological injury after cardiac arrest. Its clinical significance, prognosis and management remain a topic of discussion. Post hypoxic myoclonus was previously universally associated with a poor prognosis and was used to guide decisions regarding withdrawal of life support [7]. This theory has been challenged in recent times since the advent of therapeutic hypothermia in the management of cardiorespiratory arrest [8].

Clinical manifestations

Acute PHM is a consequence of ischemic brain injury and typically presents within 48 hours of cardiac arrest while the patient is still comatose [9]. It typically presents with rhythmic myoclonus thought to be subcortical in origin [10]. However, some studies suggest that certain cases of acute PHM, particularly those with multifocal myoclonus, may have a cortical origin and may fare better than those with subcortical myoclonus [2]. Patients with acute PHM, especially those with generalized myoclonus, are at risk for developing status myoclonus [2]. Status myoclonus refers to continuous (>30 min) or repeated generalized myoclonus and was previously associated with a grim prognosis [11], though this might no longer hold true in the era of targeted temperature management [12].

By contrast, LAS is a subcategory of myoclonus thought to be caused by hypoxic brain injury without irreversible infarction [12]. Often, patients develop the characteristic action myoclonus after return of consciousness several days to weeks after the initial hypoxic event, but LAS may also be observed within the first 96 hours of the initial insult and may precede the first signs of awareness, characteristics traditionally associated with acute PHM [3,6]. LAS was traditionally associated with cases of respiratory arrest such as status asthmaticus or airway obstruction, or in cases where a period of hypoxia preceded cardiac arrest, as was the case with our patient [13]. However, studies have also demonstrated the presence of LAS in patients with other pathologies including cardiac arrest, carbon monoxide poisoning, hemorrhagic shock, hanging and drowning [14].

It is important to differentiate between the two entities for accurate prognostication and to help guide management, though this may be a challenge: PHM was previously categorized based on the timing of onset of myoclonus, but studies have shown that acute PHM may be seen as late as 4 days after return of spontaneous circulation since the use of sedatives and therapeutic hypothermia may mask any underlying myoclonus [6]. Similarly, LAS is frequently observed after return of consciousness, though that might be hard to determine if a patient remains under sedation. Additionally, LAS was traditionally associated with onset of myoclonus days to weeks post arrest, however studies have demonstrated that it can be seen as early as 48–92 hours after arrest (also referred to as 'Early LAS') [15].

Our patient initially had generalized stimulus-sensitive myoclonus usually seen in acute PHM. She then went on to develop intention myoclonus with associated dysarthria that is typical of LAS. This suggests that she initially developed acute PHM which then progressed to LAS.

Electroencephalogram findings

EEG findings seen in acute PHM range from burst suppression, spike-wave activity, diffuse slow background, generalized periodic discharges to alpha coma [3]. More than one pattern may be present simultaneously, as seen in the case described here. In general, preserved background reactivity on EEG carries a more favorable prognosis whereas presence of any epileptiform activity, polyspike burst suppression or subcortical myoclonus might hint towards a poorer outcome [7,16].

LAS typically presents as multifocal action myoclonus, which is characteristic of cortical myoclonus [3] though LAS has also been associated with subcortical myoclonus. Focal epileptiform activity at the vertex is a defining feature of LAS, though it may also be associated with spike-wave, poly-spike activity, or slow frequency waves [15]. In fact, the presence of these findings in the acute PHM phase may hint towards progression to LAS [16].

EEG is the most reliable tool studied to help differentiate between the different presentations of PHM [3]. However, EEG findings should always be interpreted while considering other clinical findings for accurate prognostication as demonstrated in this case: Our patient's initial EEG was most consistent with diffuse voltage suppression and lack of cerebral reactivity, which would indicate a poor prognosis, though her findings were likely influenced by pharmacological sedation. Additionally, her brainstem reflexes were preserved on presentation which is a favorable prognostic sign.

Treatment

As such, there are no existing guidelines that recommend a specific treatment strategy for PHM. As demonstrated here, most treatment regimens are made based on trial and error and do not clearly differentiate between the management of various forms of PHM. Antiseizure medications (ASMs) are the mainstay of treatment for both acute PHM and LAS. The use of anesthetic agents as adjuncts may be indicated if the myoclonus interferes with medical management such as ventilator compliance. Anesthetic agents such as propofol and midazolam infusions are frequently used for symptom control but their use has not been shown to improve overall outcomes and might delay awakening [6,17].

Valproate [18] and levetiracetam [19] are most often used in the management of post hypoxic myoclonus. Perampanel is another antiepileptic agent that has been shown to reduce cortical hyperexcitability and hyper synchronization [20], which might make it especially useful in the treatment of stimulus-induced myoclonus observed in acute PHM. Zonisamide is another antiepileptic medication that is particularly effective in cortical myoclonus and has been used in patients with LAS [21]. Intrathecal baclofen has also shown some benefit in treating post hypoxic movement disorders [22].

Benzodiazepines are commonly used in the management of myoclonus. Clonazepam is the most commonly used benzodiazepine in the management of PHM including LAS. It has shown to be effective in both cortical and subcortical myoclonus [23]. Studies have demonstrated that clonazepam is superior to other benzodiazepines in the management of myoclonus. This may, in part, be due to its longer half-life, though the exact mechanism is not known [24]. Clobazam is another intermediate-acting benzodiazepine that is typically used in Lennox-Gastaut syndrome, though there are reports of its use in treating myoclonic jerks secondary to multiple other etiologies [25]. Clobazam is less sedating than other benzodiazepines which might make it a more desirable medication for long term management of myoclonus.

Our patient initially had adequate symptom control with sedatives such as propofol, ketamine and clonazepam but towards the end of her hospital stay, as she transitioned from stimulus-sensitive to intention myoclonus, these were no longer effective and she achieved better results with levetiracetam, zonisamide and baclofen. This might, in part, be explained by the difference in the pathophysiology of various forms of PHM.

PHM often requires lifelong treatment, as demonstrated by several studies [15]. Our patient continued to have significant myoclonus despite pharmacological management and eventually required physical rehabilitation. A streamlined approach towards management might help achieve adequate symptom control, improve patient satisfaction, and potentially reduce morbidity in the long run.

Conclusion

Post hypoxic myoclonus is a complex phenomenon with varied pathophysiology, clinical manifestations, prognosis, and management. PHM is generally categorized based on the timing of myoclonus, but this approach might not always be accurate as demonstrated here. Instead, it may be more accurate to consider the clinical presentation and EEG findings when differentiating between the subcategories of PHM, as demonstrated in this case. EEG is the most reliable tool studied that can help distinguish between acute PHM and LAS. As survival rates improve with advancements in post cardiac arrest care, it is important to develop a better understanding of PHM to avoid early withdrawal of care. This case also highlights the need to conduct further research into the optimal management of the various presentations of PHM.

Ethical statement

We confirm that this work is original and has not been published, nor is it currently under consideration for publication elsewhere. Informed consent was obtained from the patient whose case is outlined in our manuscript. We confirm that all authors were involved in the conception and design of this case report, drafting, and critically reviewing the manuscript and provided final approval for submission to this journal. The authors also agree to release the copyright should the manuscript be accepted for publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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