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Editorial

Post-hypoxic myoclonus: The good, the bad and the ugly

Myoclonus refers to sudden, brief, jerky, involuntary movements due to muscular contraction or interruption of muscular activity, and can be classified in a number of ways (Caviness and Brown, 2004). Clinical classification is based on the relationship to action (rest, action, reflex), body parts involved (focal, segmental, multifocal, generalized), temporal pattern (irregular, oscillatory, rhythmic) and etiology (physiologic, essential, epileptic, symptomatic). From an anatomical and neurophysiological perspective, myoclonus can be cortical, subcortical or spinal. Tests such as EEG (especially simultaneous EEG- EMG with jerk-locked back averaging), somatosensory evoked potentials and the long latency or C-reflex, are helpful in distinguishing among these types.

Etiology, anatomic origin and treatment have been relatively well established for several forms of myoclonus, particularly epileptic myoclonus. Post-hypoxic myoclonus is not as well understood, and there are several clinical challenges related to diagnosis and treatment. In addition, prognosis and decisions regarding withdrawal of medical care have been linked to the presence of acute myoclonus after cardiac arrest. This is complicated by the occurrence of different types of myoclonus in this setting – generalized, multifocal and action myoclonus (Lance-Adams syndrome) – with variable outcomes. This has important clinical implications because an inaccurate prognosis of a poor outcome can result in premature withdrawal of care, whereas an excessively optimistic prediction can lead to futile prolongation of medical treatment.

In this issue of *Clinical Neurophysiology Practice*, Freund and Kaplan (2017) discuss the clinical and neurophysiological aspects of post-hypoxic myoclonus and highlight the differences between the two major types of myoclonus that occur after cardiac arrest: myoclonus status epilepticus (MSE, also known as "myoclonic status epilepticus") and Lance-Adams syndrome (LAS). MSE occurs in comatose patients, begins within the first 72 h after cardiac arrest and usually stops after a few days. In contrast, LAS has historically been considered to begin later when patients are awake, and to be persistent (English et al., 2009). However, as pointed out by the authors, the time of onset of myoclonus and level of consciousness may not always allow clinical distinction between the two, since LAS can be seen within hours of the arrest and use of sedatives may prevent identification of the classic action myoclonus seen in LAS in the acute stage. The pattern of involvement of body parts may also not be helpful, since generalized or multifocal myoclonus can occur in both forms. Because of a possible difference in the outcome for generalized compared to multifocal MSE, some groups (van Zijl et al., 2016) have attempted to identify clinical features separating the two, such as proximal (generalized) versus distal, periocular or perioral (multifocal) body part involvement. Freund and Kaplan (2017) appropriately suggest caution in using such criteria unless they are validated by further studies.

There are no standard treatment guidelines or large clinical trials for MSE or LAS. Response to treatment is largely based on anecdotal evidence and the presumed origin (cortical or subcortical). Antiepileptic drugs, benzodiazepines, anesthetic agents and serotonergic drugs (5-HTP, methysergide) have been used for both conditions (Gupta and Caviness, 2016; Freund and Kaplan, 2017).

If clinical evaluation and response to treatment are not helpful in differentiating between MSE and LAS, can neurophysiological tests provide answers? Cortical myoclonus is characterized by jerk-locked epileptiform discharges on EEG, giant SSEPs and a cranio-caudal progression of activation of muscles on EEG-EMG polygraphy. On the other hand, in patients with subcortical or brainstem myoclonus, there is neither jerk-locking nor giant SSEPs, and EEG-EMG polygraphy shows initial activation of muscles innervated by lower brainstem nuclei (such as the sternocleidomastoid) followed by facial and arm muscles (Hallett et al., 1977). Studies in post-hypoxic patients have shown conflicting results, and it remains unclear whether the myoclonus is cortical or subcortical in origin. As suggested by Freund and Kaplan (2017), it is possible that generalized MSE is more likely subcortical, and that multifocal MSE and LAS are cortical. Some patients can have a mixed pattern of cortical and subcortical myoclonus due to hypoxic injury to multiple structures (Gupta and Caviness, 2016).

There are several clinical difficulties in performing neurophysiological tests in the acute post-hypoxic patient, but they are more feasible in chronic LAS. As noted by Gupta and Caviness (2016) in their systematic review of post-hypoxic myoclonus, there are few studies using EMG and other neurophysiological techniques in MSE, and EEG is by far the most commonly used test. There is no single EEG finding specific for MSE, but abnormalities tend to be diffuse (burst-suppression, generalized epileptiform or periodic discharges, diffuse slowing). An important point made by Freund and Kaplan (2017) is that EEG findings can change over time. In patients with MSE, Elmer et al. (2016) observed a stereotyped evolution (Pattern 1), consisting of four stages: initially burst-suppression with high amplitude polyspikes, then longer burst duration with lower amplitude of polyspikes, followed by loss of amplitude and complexity, and finally generalized periodic discharges progressing to diffuse attenuation. None of the patients with this pattern had a favorable outcome. LAS can also be associated with nonspecific findings such as diffuse or focal slowing and even normal EEGs. However, many patients have focal spikes or polyspikes, with jerk-locking demonstrating a spike over the appropriate sensorimotor cortex or vertex preceding the jerk (Gupta and Caviness,

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2016; Freund and Kaplan, 2017). This has not been shown to occur in MSE. The recent observation (Elmer et al., 2016) that vertex-localized spikes can be seen in a proportion of patients as early as 6–8 h after CA and often predict a relatively favorable outcome with development of LAS, makes it a particularly valuable tool for early prognostication.

Freund and Kaplan (2017) provide a comprehensive review of a confusing and poorly understood topic that is nevertheless of great clinical importance. This article would have been further enhanced by a brief discussion or commentary on the impact of therapeutic hypothermia on the clinical and neurophysiological findings, as well as prognosis. Therapeutic hypothermia has been shown to improve survival and neurological recovery after cardiac arrest and has become the standard of care. Rossetti et al. (2010) found that, in patients undergoing therapeutic hypothermia, some clinical features, including impaired motor response to pain and myoclonus may not be as reliable in predicting a poor outcome as previously thought. They also noted that the presence or absence of EEG background reactivity was helpful in predicting the outcome.

Clinicians are faced with the dilemma of distinguishing between "good" (LAS) and "bad" (MSE) myoclonus in the acute post-cardiac arrest setting in order to avoid the "ugly" situation of either a self-fulfilling prophecy from premature withdrawal of care or unnecessary prolongation of treatment. The American Academy of Neurology (AAN) practice parameter on prediction of outcome in comatose survivors after cardiopulmonary resuscitation (Wijdicks et al., 2006) indicates that patients with MSE invariably have in-hospital deaths or a poor outcome, even if they have intact brainstem reflexes or some motor response. Wijdicks et al. (1994) have also previously stated that the presence of MSE in comatose patients after cardiac arrest must strongly influence the decision to withdraw life support. However, the situation has become more complicated with the use of therapeutic hypothermia, as the outcome for MSE may not always be so dismal. Moreover, as this review suggests, some patients previously thought to have MSE may actually have LAS with a more favorable outcome, since LAS can occur within the first 24 h even in comatose patients. It would therefore be prudent for clinicians to use caution in applying the AAN criteria in the era of therapeutic hypothermia. There is growing evidence to suggest that acute post-hypoxic myoclonus should not be used as the only criterion for prognosis and decisions regarding treatment withdrawal.

Given the great difficulty in making a clinical distinction between MSE and LAS in the acute setting, neurophysiological studies, particularly EEG, are important and can influence clinical decision-making in several ways. Because of temporal changes in EEG findings, serial or, preferably, continuous EEGs should be performed. As suggested by Rossetti et al. (2010), EEG background reactivity may be important for prognostication in patients undergoing hypothermia. Evolution such as that observed with Pattern 1 (Elmer et al., 2016) may portend a grim outcome. If LAS can be reliably diagnosed in the acute setting by the presence of focal spikes localized to the vertex, this would provide an early and objective indication of a more favorable outcome. Larger studies confirming these observations or identifying other neurophysiological parameters that may determine the type of myoclonus and outcome in this population are urgently needed.

Conflicts of interest and funding sources

None.

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