Movement Disorders after Resuscitation from Cardiac Arrest

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Those who survive cardiac arrest often experience significant neurologic impairment. A rare, but often debilitating, consequence of cardiac arrest is the development of movement disorders. A wide range of movement disorders, with many different causes, is observed after cardiac arrest. Cardiac arrest survivors may develop movement disorders from metabolic disturbances resulting from hypoxic-ischemic damage to the liver or kidney, from medications administered to treat other complications of cardiac arrest, or from cardioembolic ischemic stroke as a result of impaired myocardium or cardiac valves. This review focuses on movement disorders caused by cerebral hypoxia after cardiac arrest. Many different movement disorders are described after hypoxic-ischemic brain injury, including parkinsonism, dystonia, chorea, tics, athetosis, tremor, and myoclonus [1–5]. Of these movement disorders, the one reported and investigated most extensively is posthypoxic myoclonus (PHM). Hence, this article describes the clinical spectrum, pathophysiology, and treatment of PHM before briefly discussing other posthypoxic movement disorders.

**Posthypoxic myoclonus**

Myoclonus refers to sudden, shock-like, involuntary movements that can manifest in various patterns. Myoclonus may be focal, where a few adjacent muscles are involved; multifocal, where many muscles jerk asynchronously; or generalized, where most of the muscles of the body are involved in
synchronized fashion. Additionally, myoclonic movements may be spontaneous or they may be activated by either movement or sensory stimulation. Finally, myoclonus may be comprised of “positive” movements, in which a burst of electromyographic activity is associated with the movement, or negative movements, in which a brief pause of tonic muscular activity leads to a jerk [6,7].

The causes of myoclonus are many. In 1963, however, Lance and Adams described four patients who developed severe myoclonus after surviving cardiac arrest [8]. These patients initially developed a generalized myoclonus accompanied by dysmetria, dysarthria, and ataxia. Over time, the myoclonus persisted but its character changed to a predominantly action myoclonus involving the limbs. Lance and Adams hypothesized that this particular constellation of symptoms observed after cardiac arrest was the result of cerebral hypoxia [8]. Since this initial description, more than 40 years ago, more than 100 patients who have had PHM have been reported in the medical literature [9–11], many of whom suffered hypoxia from cardiac arrest. Concordant with the initial descriptions by Lance and Adams, it is recognized that there are two types of PHM: acute PHM, which occurs soon after a hypoxic insult and is characterized by generalized myoclonus; and chronic PHM (Lance-Adams syndrome), which begins after a period of delay and is manifested predominantly by action myoclonus.

Acute posthypoxic myoclonus

Acute PHM occurs soon after a hypoxic episode and is characterized by severe, generalized myoclonic jerks in patients who are deeply comatose [7]. The jerks begin typically within the first 24 hours after hypoxia and often are characterized by violent flexion movements. When they persist for more than 30 minutes or occur for most of the first postresuscitation day, some term the abnormal movements, myoclonic status epilepticus (MSE), despite the lack of definitive evidence that these movements represent epileptic activity. Posthypoxic MSE occurs in approximately 30% to 40% of comatose adult survivors of cardiopulmonary resuscitation and is difficult to control and associated with a poor prognosis. In the largest published series of posthypoxic MSE, Wijdicks and colleagues find that all 40 patients had intermittent generalized myoclonus involving both face and limb muscles. Stimuli, such as touch, tracheal suctioning, and loud handclaps, triggered myoclonic jerks in most of the patients. None of the 40 patients who had acute posthypoxic MSE awakened, improved in motor response, or survived [12]. In another review of 18 patients who had posthypoxic MSE, 14 patients died within 2 weeks and the two patients who survived were left with profound disability [13]. A meta-analysis of patients who had posthypoxic MSE paints a similarly grim picture: of 134 pooled cases, 119 (88.8%) died, 11 (8.2%) remained in a persistent vegetative state, and 4 (3.0%) survived. Of the four patients who survived, two were described as having a good outcome [13].
Clues to the pathophysiology of acute PHM arise from electrophysiologic and histopathologic studies. The electroencephalograms (EEGs) in these patients are variable, but often display bursts of generalized spikes and poly-spikes or a burst suppression pattern, believed to be consistent with severe neuronal injury. On autopsy, patients who have acute posthypoxic MSE have evidence of neuronal ischemia and cell death in the cerebral cortex, deep gray nuclei (ie, basal ganglia and thalamus), hippocampus, and cerebellum [13]. Cortical damage is more severe in patients who have MSE than in those who do not have myoclonus, however [14]. Because the severity of cortical damage implies that the cortex may not be capable of generating any activity, including myoclonic activity, it is postulated that acute PHM arises from a brainstem generator [7].

Treatment of myoclonic jerks in acute PHM is difficult and of questionable usefulness, particularly in the setting of posthypoxic MSE. Multiple medications often are used, the most common of which are phenytoin, valproate, and benzodiazepines. In one study of 18 patients who had posthypoxic MSE, 13 patients required intravenous anesthetic agents, including propofol and midazolam [13]. Despite aggressive treatment of the myoclonic jerks, poor prognosis resulting from the severity of underlying brain injury is the rule rather than the exception.

Chronic posthypoxic myoclonus—Lance-Adams syndrome

Chronic PHM, also known as Lance-Adams syndrome, typically occurs within a few days to a few weeks after hypoxic injury. In a series of 14 patients who had chronic PHM, all but one were noted to have the onset of myoclonus while still in coma [9]. The myoclonus has several characteristic features. Patients have an action myoclonus involving predominantly the limbs. Myoclonic jerks commonly appear immediately on attempting to move or position a limb and occasionally spread to other portions of the body. The jerks generally disappear with relaxation of the limb. The precision of the motor task seems to be proportional to the severity of myoclonus, making everyday tasks, such as bringing a cup to the mouth or grasping a small object, extremely difficult [8,10,11]. In addition, the myoclonus of chronic PHM has several other distinctive characteristics. In their series of 14 patients, Werhahn and colleagues report that 11 had stimulus-sensitive myoclonus [9]. Negative myoclonic jerks also contribute significantly to morbidity in patients who have chronic PHM. Postural lapses resulting from negative myoclonus predispose patients to frequent falls and often result in patients being confined to wheelchairs [10].

Chronic PHM is a syndrome with diverse clinical, electrophysiologic, and neurochemical abnormalities [7,10], and the pathophysiology of this condition is poorly understood. An example of the diversity of the disorder lies in the nature of the myoclonus itself. The myoclonus in chronic PHM may have a cortical or subcortical origin. Clinical clues suggestive of a cortical
origin include myoclonus that is distally predominant, highly action induced, and stimulus sensitive. A cortical origin for myoclonus also is supported by electrophysiologic measures, such as enlarged somatosensory evoked potentials and the gold standard, back-averaged EEG. Using such measures, it seems that cortical myoclonus is much more common in chronic PHM than subcortical myoclonus, the latter of which tends to cause violent jerks of the proximal limbs and trunk [10]. Patients who have chronic PHM, however, may suffer from cortical myoclonus, subcortical myoclonus, or a combination of the two, and there are no prognostic factors that can predict which subtype of myoclonus a patient will develop.

The neurochemical and anatomic bases of chronic PHM remain unclear. Several lines of evidence suggest that specific neurotransmitter abnormalities are involved in the pathogenesis of chronic PHM. Isolated reports demonstrate that low levels of 5-hydroxyindole amino acid (5-HIAA), a serotonin metabolite, are present in the cerebrospinal fluid of patients who have PHM [15]. Some patients who have chronic PHM improve with administration of the serotonin precursor, 5-hydroxytryptophan (5-HTP) [16]. Further support for a role of the serotonergic system in chronic PHM comes from animal models. Several groups demonstrate that, in rat models of PHM, myoclonus improves with 5-HTP treatment and severity of myoclonus correlates inversely with levels of striatal serotonin and cortical 5-HIAA. In addition, direct modulation of serotonin receptors affects PHM, as demonstrated in animal models in which the administration of agonists and certain antagonists of serotonin receptors can ameliorate PHM [17–20].

Another clue that serotonin signaling may be involved in the pathophysiology of PHM lies in the finding that the majority of patients in the largest published series on PHM are female. A recent study examines the role of estrogen in PHM and finds that estrogen treatment of female rats that were ovariectomized resulted in a significant increase in intensity and duration of PHM [21]. It is hypothesized that estrogen, through its regulation of serotonergic activity, may influence the clinical course of PHM. Thus, it seems that although serotonergic modulation affects PHM, the relative contributions of serotonin metabolism and of specific serotonin receptors to the overall mechanisms of PHM remain unclear.

A recent report that describes marked exacerbation of chronic PHM in a patient administered trimethoprim-sulfamethoxazole (TMP-SMX) may implicate phenylalanine, a neurotransmitter precursor, in the pathogenesis of PHM. A patient who had high-grade non-Hodgkin’s lymphoma and chronic PHM whose myoclonus was well treated with oral piracetam developed marked worsening of myoclonus on exposure to high-dose intravenous TMP-SMX. A reduction of the dosage of TMP-SMX resulted in a dramatic and rapid improvement of the myoclonic jerks [22]. The investigators believed it unlikely that alterations of renal or hepatic metabolism, or pharmacokinetic or pharmacodynamic interactions between TMP-SMX and piracetam, accounted for the worsening of myoclonus; rather, they hypothesized that
TMP-SMX may have resulted in increased myoclonus by its well-described action of impairing phenylalanine metabolism and, thereby, elevating phenylalanine levels. Elevated phenylalanine levels, in turn, are linked to several neurologic conditions. Unfortunately, neither serum nor cerebrospinal fluid phenylalanine levels were obtained to support this hypothesis.

Recently, radiologic tools have been used in an attempt to understand the anatomic and pathophysiologic basis of PHM. Seven patients who had chronic PHM and EEG back averaging that demonstrated cortical myoclonus underwent fluorodeoxyglucose–positron emission tomographic scanning. Compared with control subjects, patients who had PHM exhibited significant increases in glucose metabolism in several brain regions, including the ventrolateral thalamus [23]. Such findings may be compatible with the rat PHM model, in which the ventrolateral thalamic nucleus is implicated indirectly in the pathogenesis of PHM; Purkinje cell death occurs selectively in the paravermal and vermal areas, which project mainly to the dorsolateral protuberance of the fastigial nucleus and, in turn, to the ventrolateral thalamic nucleus [24]. Thus, there may be a link between the Purkinje cell death seen in PHM rats and the increased metabolic uptake observed by PET scanning in the ventrolateral thalamic nucleus of humans who have PHM.

The treatment of chronic PHM can pose a challenge for several reasons. As previously alluded to, chronic PHM is a syndrome with diverse clinical presentations likely stemming from varied pathophysiologies. In addition, the effect of many drugs reported in the literature is given in qualitative fashion, providing only an approximation of an agent’s efficacy. Also, the small number of patients who develop this syndrome obviates the possibility of large-scale clinical trials to evaluate the efficacy of antmyoclonic agents. Despite these difficulties, a recent review of the literature, which includes more than 100 cases of PHM, supports several important conclusions. Clonazepam, valproate, and piracetam demonstrate significant efficacy in approximately 50% of patients in whom these agents were instituted. Therefore, the authors consider these to be first-line agents in the treatment of chronic PHM. A role for 5-HTP also is supported by the authors’ recent literature review. 5-HTP resulted in marked or full improvement in 40% of patients in whom the effect was reported; however, concomitant treatment with carbidopa often is necessary to prevent the severe nausea that accompanies administration of this drug. Several other drugs, including baclofen, diazepam, ethanol, and methysergide, also are reported as efficacious in a limited number of patients. An analysis of these 122 cases reveals that there are several drugs that were reported to be not significantly efficacious in any case of chronic PHM; these include phenytoin, primidone, phenobarbitol, and tetrabenazine [10].

Several newer agents also are reported to have efficacy in the treatment of chronic PHM. Levetiracetam, chemically related to piracetam, has been studied by several groups of investigators. Krauss and colleagues note that one of two patients who had chronic PHM experienced substantial improvement in myoclonus, whereas the other experienced some improvement.
with doses of 500 to 750 mg twice daily [25]. Another study of the effects of levetiracetam on myoclonus of different causes notes that rapid and sustained symptomatic improvement occurred only in a single patient who had chronic PHM [26]. The authors also have studied the efficacy of levetiracetam in PHM. They conducted an open-label, dose-escalation trial of this medication in seven patients who had chronic myoclonus (including three who had posthypoxic myoclonus) and showed that the mean Unified Myoclonus Rating Scale scores trended downward in every section after administration of levetiracetam, with significant decreases in the sections addressing patient self-assessment and physician assessment of global disability [27].

Several reports describe patients who have PHM experiencing improvement of myoclonus with administration of alcohol [28,29]. Based on a previous report that a patient who had alcohol-responsive myoclonus-dystonia had significant improvement when treated with γ-hydroxybutyric acid (GHB) [30], the authors recently studied the efficacy of GHB in one patient who had alcohol-responsive chronic PHM. Using an open-label, dose-finding, blinded-rater approach, they found that oral GHB was markedly effective in ameliorating severe alcohol-sensitive PHM in this single patient [31].

Regardless of treatment, the majority of patients who have chronic PHM improve over time. Myoclonus, ataxia, and speech all tend to improve over several years, and disability scores reflective of the ability to ambulate, communicate, and take care of themselves also improve [8,9]. In one series of 14 patients who had chronic PHM, only four patients did not have an improvement in global disability score at a mean follow-up of 3.7 years [9]. Although many patients do experience significant improvement in symptoms, some who have chronic PHM remain significantly disabled despite medical therapy. Currently, there are no well-accepted surgical options for such patients. The authors hypothesize, however, that, given the ventral thalamic hypermetabolism observed on PET scan in these patients and the fact that thalamotomy and thalamic stimulation are applied successfully to single patients who have intractable myoclonus, stereotactic targeting of the ventrolateral thalamus using deep brain stimulation may be appropriate in some patients who have severe, medication-refractory chronic PHM [23].

Other posthypoxic movement disorders

A variety of other movement disorders are observed after cerebral hypoxia, including parkinsonism, dystonia, chorea, athetosis, and tremor [1–5]. Although PHM may result from injury to the cerebellum or thalamus, many of these other movement disorders are caused by damage of the basal ganglia. Dystonia is one of the more common movement disorders to occur after cerebral hypoxia and may develop in combination with an akinetic-rigid (parkinsonian) syndrome. This article discusses the clinical spectrum of posthypoxic dystonic and akinetic-rigid syndromes and focuses on the pathophysiology of basal ganglia dysfunction in these conditions.
Dystonic and akinetic-rigid syndromes, alone or in combination, represent a sizeable proportion of the posthypoxic movement disorders described in the literature. Many of these cases are reported in patients surviving cardiac arrest. These syndromes may occur acutely, either at the time the hypoxic insult occurs or shortly thereafter, or more commonly in delayed fashion, months to years after the initial hypoxic insult [32]. The posthypoxic akinetic-rigid syndrome usually is a symmetric condition characterized by various combinations of bradykinesia, micrographia, axial and appendicular rigidity, resting or postural tremor, and marked postural instability [3,33]. Posthypoxic dystonia can affect the limbs and face and often is asymmetric at onset with progression to a symmetric, generalized dystonia. In a review of 12 patients who previously were normal and who suffered hypoxic ischemic insults of various causes, including cardiac arrest, Marsden and colleagues note that six of the patients developed a pure dystonic syndrome, two developed a pure akinetic-rigid syndrome, and four initially developed an akinetic-rigid syndrome followed later by a dystonic syndrome [34]. The akinetic-rigid syndrome developed typically within 3 months of the hypoxic event; after a rapid evolution, the majority of patients remained clinically stable for many subsequent years. In contrast, the pure dystonic syndrome developed, on average, 10 months after the hypoxic event, and progressed gradually over several years. The majority of patients had visible lesions in the basal ganglia on brain CT or MR imaging. Treatment of akinetic-rigid symptoms with levodopa or dopamine agonists and administration of high-dose anticholinergic drugs for dystonic symptoms conferred little benefit to these patients.

Why do some patients who have basal ganglia lesions after cerebral hypoxia develop an akinetic-rigid syndrome, whereas others develop a predominantly dystonic syndrome? Marsden and colleagues note that the mean age of the akinetic-rigid group at the time of anoxia was 41 years, whereas that of the pure dystonic group was 13.5 years. Indeed, all six patients who developed a pure dystonic syndrome were ages 21 years or less. This observation led to the hypothesis that an age-dependent difference in the clinical manifestations of hypoxia exists, with younger people more prone to dystonia and older individuals more prone to an akinetic-rigid state [33]. Such age-dependent differences also are observed in conditions, such as Parkinson’s disease, in which early-onset patients are predisposed to dystonia. A mechanistic understanding of these observations, however, remains elusive.

The location of brain injury within the basal ganglia seems to be another factor that governs whether or not patients develop dystonia versus an akinetic-rigid state after cerebral hypoxia. Hawker and Lang, in their case series of three patients who had suffered cerebral hypoxia, note that the two patients who had primarily dystonic syndromes had lesions of the putamina on head CT, whereas the patients who had an akinetic-rigid syndrome had marked bilateral lesions of the globus pallidus. Similar clinicanoatomic associations are found in a wide variety of insults to the basal ganglia,
including trauma, neurodegenerative diseases, and encephalitides [4]. This has led to the proposal that in the setting of hypoxia, lesions of the globus pallidus are responsible for the akinetic-rigid syndrome, whereas lesions of the putamen account for dystonia [2]. Further support for this hypothesis is provided by Marsden and colleagues, who find that dystonia is associated with putaminal injury in 10 of 14 cases and an akinetic-rigid syndrome is associated with globus pallidus lesions in 11 of 14 cases. This association is not absolute, however, as several examples of dystonia associated with pallidal lesions and parkinsonism associated with putaminal lesions are noted [33].

Two other questions arise with respect to the pathophysiology of hypoxia-induced basal ganglia lesions. First, why are the basal ganglia so vulnerable to hypoxic insults? Two main hypotheses are put forth to explain this selective vulnerability. The “vascular hypothesis” states that selective hypoperfusion results from the vascular supply of the basal ganglia and, in particular, the globus pallidus, underlies its susceptibility to hypoxic injury. The second theory is the “metabolic hypothesis,” which postulates that factors intrinsic to the striatum, such as intrinsically high oxidative metabolism or high density of excitatory amino acid receptors, results in hypoxic damage [2,34]. Further studies are needed to determine whether or not vascular, metabolic, or other factors underlie the susceptibility of the basal ganglia to hypoxic injury. The second main question that arises is, how can a single exposure to cerebral hypoxia lead to the delayed onset and progression of symptoms years later? Several mechanisms, including aberrant sprouting, synaptic reorganization, ephaptic transmission, and inflammatory changes, are suggested as possible mechanisms of delayed symptomatology. Parallels with other neurodegenerative diseases, in which excitotoxicity is followed by mitochondrial dysfunction, oxidative stress, and eventual neuronal apoptosis, also are speculated to play a role [34,35]. Regardless of the mechanism, it seems that damage to the basal ganglia with preservation of the pyramidal system is a pathologic correlate of delayed posthypoxic dystonia or akinetic-rigid syndromes [36].

Summary

It is difficult to predict precisely the final neurologic outcome from cardiac arrest and accompanying cerebral hypoxia. Although rare, several movement disorders may arise as a consequence of hypoxic injury, including myoclonus, dystonia, akinetic-rigid syndromes, tremor, and chorea. Dysfunction of various portions of the central nervous system, including the basal ganglia, thalamus, midbrain, and cerebellum, is implicated in the pathogenesis of these posthypoxic movement disorders. The development of animal models of posthypoxic movement disorders and of newer imaging techniques applied to human patients who have movement disorders after hypoxic episodes has improved understanding of the pathophysiology of posthypoxic movement disorders and has suggested newer treatments.
Many outstanding questions remain, however. What factors promote susceptibility to the development of posthypoxic movement disorders? Why do patients who have similar clinical hypoxic insults develop markedly dissimilar movement disorders? Why are the basal ganglia especially vulnerable to cerebral hypoxia? Why do some movement disorders occur in delayed fashion and progress for years after the hypoxic insult? Is the pathogenesis of progressive posthypoxic movement disorders related to that of neurodegenerative diseases? What are the most effective medications for the various posthypoxic movement disorders? Is there a role for deep brain stimulation in the treatment of posthypoxic movement disorders? We anticipate that current and future research in the area of posthypoxic movement disorders will reveal answers to some of these important questions.

References


