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Case Report

Tetrabenazine in Delayed Post Hypoxic Choreoathetosis after Resuscitation from Cardiac Arrest

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Abstract

Background: After cardiac arrest (CA), global cerebral ischemia results in brain tissue damage, inducing post-anoxic movement disorders (PMD) in some survivors. There are no current consensus recommendations to treat refractory PMD.

Case Report: A 72-year-old male, smoker, presented with confusion, fever, and dyspnea. Progressive respiratory failure led to hemodynamic compromise and subsequent CA. He was resuscitated for 15 minutes but remained in a vegetative state. Magnetic resonance imaging (MRI) was normal and serial electroencephalograms were uncontributive. Median nerve somatosensory evoked potentials showed normal N20 waves. Six weeks after CA, while in a persistent vegetative state, the patient developed myoclonus and choreoathetosis requiring the resumption of sedatives to avoid ventilator asynchronies. A significant reduction in PMD was obtained with tetrabenazine, allowing withdrawal of the sedatives.

Conclusion: In our case, tetrabenazine seemed to provide a better effect than other current medications (including levomepromazine) in PMD, allowing sedation and respiratory support withdrawal.

Keywords: Cerebral hypoxia; Movement disorders; Tetrabenazine

Introduction

Sudden cardiac arrest (CA) is the third leading cause of death in Europe [1]. A pause in cerebral circulation can deplete neuronal oxygen stores within 20 seconds, leading to loss of consciousness, followed by depletion of brain glucose and ATP stores. Just 15 minutes after cardiac arrest, global cerebral ischemia results in damage of up to 95% of brain tissue [2].

The mechanisms of brain injury, as well as the prognosis, are not the same in every patient and some survivors may develop movement disorders secondary to hypoxic injury, including myoclonus, parkinsonism, dystonia, chorea, athetosis, and tremor [3, 4]. Potential therapeutic options have been explored; however, there are no current consensus recommendations to treat refractory post-anoxic movement disorders.

We report a case of post-CA hypoxic encephalopathy with delayed choreoathetoid movements that improved with tetrabenazine after oral levomepromazine failure, allowing sedation withdrawal.

Case Report

A 72-year-old man with severe COPD was transferred to our hospital due to fluctuating confusion, fever, and dyspnea. On examination, there was no sensory or motor deficit. Initial brain computed tomography (CT) detected no abnormality. Cerebrospinal fluid (CSF) was acellular and cultures were negative, but multiplex PCR (meningitis encephalitis panel) of the CSF was initially positive for herpes virus (HSV1). Brain magnetic resonance imaging (MRI) was normal and serial electroencephalograms (EEG) were also normal. A repeated CSF fluid analysis revealed no cells; cultures and multiplex PCR, including herpes virus, were found negative. Brain imaging controls were not contributive.

During hospitalization, the patient's pulmonary status deteriorated, resulting in hemodynamic compromise and subsequent CA. He was resuscitated for approximately 15 minutes and after complete return of spontaneous circulation (ROSC), neurological examination revealed no spontaneous eye-opening and no response to painful stimuli, though the pupils were myotic and reactive. Mild hypothermia (under 36°C) with deep sedation to optimize mechanical ventilation and neuroprotection was initiated.

The patient remained in a vegetative state after stopping all sedative and paralytic medications. Seizures, postictal encephalopathy, electrolyte abnormalities, and metabolic derangements were ruled out. A follow-up CT of the head showed only a slight ischemic lesion in the cerebellum. Consecutive EEGs demonstrated no status epilepticus or epileptic discharges. Neuron-specific enolase levels were mildly elevated at 72 ng/mL (normal value < 16 ng/mL).

Brain MRI confirmed the small cerebellar ischemic lesion. Median nerve somatosensory evoked potential showed normal N20 waves. Brain positron emission computed tomography (PET) found prefrontal, parietal, occipital, and cerebellar hypo metabolism.

Six weeks after ROSC, the patient remained in a persistent vegetative state and developed post-anoxic movement disorders (myoclonus and choreoathetosis) requiring the resumption of sedatives to avoid ventilation difficulties.

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A trial of levomepromazine 100 mg daily for the choreoathetoid and myoclonic movements was unsuccessful. He was subsequently treated with tetrabenazine, leading to a significant reduction in the amplitude and frequency of movements after 20 days of treatment, without side effects, allowing sedative and ventilation withdrawal.

Discussion

After CA, many complex physiological and molecular events occur, resulting in significant brain damage. They are well-described by Sekhon [5] and Sandroni [6] in a "*two-hit*" model theory. In this model, primary injury occurs from immediate cessation of cerebral oxygen delivery (CDO_2) during CA, and secondary injury occurs after resuscitation.

The consequence of decreased oxygen in the brain is decreased ATP production, as well as membrane ATP-dependent Na-K pump dysfunction, and accumulation of intracellular Na^+ with the subsequent cytotoxic edema. This alteration of cellular integrity called excitotoxic injury [7] stimulates excessive glutamate release, which favors a massive influx of calcium into the cell, activation of many enzymes, and consequent cellular damage.

During the secondary injury, or reperfusion phase, paradoxically the restoration of blood flow and tissue oxygenation result in complex enzymatic oxidation reactions producing free radicals that contribute to cell death [8]. An additional consequence of acute reperfusion is the blood-brain barrier disruption, with permeability increase and leukocyte migration, which also leads to vasogenic edema.

Brain reperfusion after transient global ischemia is incomplete and inhomogeneous. Some areas in the brain are most vulnerable, such as the cerebral cortex, hippocampus, and cerebellar Purkinje cells [9]. Some other regions, such as the basal ganglia and cerebellum, have been implicated in the emergence of movement disorders and discoordination [10]. On the other hand, hypoxia-relative preservation of the brainstem, instead of impairment of the cortex and thalamus, results in vegetative and comatose states.

Post-hypoxic myoclonus (PHM) is the best-described abnormal movement following CA [11]. In PHM, the myoclonus appears within the first 24 hours after CA, often in comatose patients, and is usually associated with poor prognosis [12].

In chronic PHM (Lance-Adams syndrome), the movement disorders emerge a few days to several weeks following CA and rarely in comatose patients. A cortical origin has been proposed [6].

Other post-hypoxic movement disorders (PMD), including dystonia, ballism, choreoathetosis, or a kinetic rigid syndrome have been reported [13].

Dystonia associated with parkinsonism or chorea appears within 3 months after the hypoxic event. In contrast, pure dystonic syndrome appears later around 10 months after CA and progresses over the time. Some lesions in the basal ganglia can be seen on brain imaging [12].

Three main neurotransmitter systems are involved in PMD:

Cholinergic system: Hypoxia-induced hyperactivity of the cholinergic interneurons intrinsic source of acetylcholine (Ach) to the striatum. Improvement of dystonia is obtained with anticholinergic drugs.

GABAergic system: During hypoxia, a selective GABAergic deficit on the level of synapse has been described that could account for the frequent occurrence of myoclonus and seizures after hypoxic insults [14]. Baclofen is a GABA agonist and benzodiazepines are GABAergic medications.

Dopamine system: Striatal dopamine increases rapidly during global cerebral hypoxia. To reduce dopamine levels, dopamine depletory (such as tetrabenazine (TBZ)) or dopamine-blocking drugs (clozapine and neuroleptics) are used. TBZ reduces the transport of dopamine to the presynaptic vesicles providing benefits in dystonia.

The use of TBZ in the treatment of hyperkinetic movement disorders, particularly in tardive dyskinesia and chorea, it is supported by high-level evidence [15].

Scheibe [16] followed 12 patients with PMD, of which seven were associated with chronic hypoxic myoclonus. Final control of PMD was best achieved by TBZ in the case of choreoathetosis and ballism, and by levodopa/benserazide in kinetic rigid symptoms. All PMD responded to intrathecal baclofen with a limited response. Remarkably, haloperidol and olanzapine result in massive exacerbation of dystonia.

In our patient who remained in a vegetative state, TBZ reduced generalized dystonia and choreoathetoid movements after failure of oral levomepromazine. The starting dose was 12.5 mg daily and progressively increased to 75 mg daily. The adverse effects of TBZ are depression, fatigue, parkinsonism, and somnolence. In our case, no side effects and no changes in the corrected QT interval were noticed. After 20 days, abnormal movements were clearly reduced, allowing sedation and mechanical ventilation withdrawal.

Conclusion

Tetrabenazine seems to provide a more beneficial effect than levomepromazine in some PMD. Considering this case report, TBZ should probably be used directly to control PMD, allowing sedation and respiratory support withdrawal. Large studies are needed to corroborate this finding.

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