CASE REPORT

Morphine: An Effective Abortive Therapy for Pediatric Paroxysmal Sympathetic Hyperactivity After Hypoxic Brain Injury

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Paroxysmal sympathetic hyperactivity (PSH) is a life-threatening condition characterized by hyperadrenergic activity and autonomic dysfunction. Also termed *autonomic storms*, PSH can occur after a variety of cerebral insults, most commonly traumatic brain injury. Limited pediatric literature is available, especially in patients with brain injury from hypoxia. No consensus exists for the terminology, diagnostic criteria, or treatment algorithm for PSH. Thus, the optimal management, including medication selection and dosing, remains unclear. We present the detailed treatment of a 9-year-old, African American male with hypoxic brain injury after pulseless arrest following status asthmaticus, who subsequently developed PSH. The patient began to experience episodes of tachycardia, hypertension, tachypnea, diaphoresis, rigidity, and dystonic posturing on hospital day 5. After ruling out other potential causes, a diagnosis of PSH was made. Episodes of PSH failed to respond to lorazepam or labetalol but were aborted successfully with morphine. Management of PSH after hypoxic brain injury required medications for acute treatment as well as for prevention of PSH. Morphine was found to be highly effective and safe for aborting the autonomic crises. Other agents more commonly described in the literature did not result in an adequate response and were associated with significant adverse effects. A combination of clonazepam, baclofen, and either propranolol or clonidine aided in reducing the frequency of episodes of PSH. We suggest using morphine for aborting severe episodes of PSH that do not respond to antihypertensive agents or benzodiazepines.

INDEX TERMS: autonomic nervous system diseases, brain injuries, morphine, pediatrics

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INTRODUCTION

Paroxysmal sympathetic hyperactivity (PSH), a condition characterized by hyperadrenergic activity and autonomic dysfunction, has been reported following acute brain injury and other cerebral insults.[1–3] In addition, PSH is described as episodic periods of excessive autonomic activity, manifested by tachycardia, hypertension, tachypnea, fever, diaphoresis, dystonic posturing, and rigidity.[3] A variety of neurologic injuries may result in PSH, with most reports found in the traumatic brain injury (TBI) population.[2] Limited pediatric literature is available, especially in patients with brain injury from hypoxia. No consensus exists for the terminology, diagnostic criteria, or treatment algorithm for PSH. Consequently, most management strategies are based on evidence from small studies and case reports.[1,4–13] Here, we describe the detailed treatment of a 9-year-old male with severe PSH following hypoxic brain injury that was intractable to reported therapies, including α-adrenergic agonists, β-adrenergic blockers, and benzodiazepines. Multiple episodes of autonomic crises were successfully aborted with morphine.

CASE REPORT

A 9-year-old, 34-kg African American boy ex-

perienced a pulseless arrest from status asthmaticus lasting longer than 10 minutes and required intubation. His neurologic examination revealed responsive pupils and a positive gag reflex but no response to voice or noxious stimuli. The patient also had extensor posturing movements with suctioning and neck stimulation. Magnetic resonance imaging revealed findings consistent with hypoxic brain injury.

Fentanyl and midazolam continuous infusions were initiated for analgesia and sedation, but he was weaned and medications were discontinued on hospital days 2 and 3, respectively, to better assess neurologic status. Starting on hospital day 4, the patient had periodic episodes of tachycardia, hypertension, dystonic posturing, fever, muscle rigidity, and dilated pupils. Symptoms were thought to be due to opioid and/or benzodiazepine withdrawal, thus fentanyl and midazolam continuous infusions were restarted on hospital day 5. Because of this clinical deterioration, a computed tomography scan was obtained and revealed severe cerebral edema. Management to reduce intracranial pressure was initiated, including hyperventilation, hypertonic saline, mannitol, and vecuronium. Initially, the autonomic instability was attributed to increased intracranial pressure, but symptoms worsened rather than improved as the cerebral edema resolved. Drug withdrawal was eventually ruled out because symptomatic episodes continued despite reinitiation of fentanyl and midazolam; thus, fentanyl and midazolam were tapered and discontinued on hospital days 10 and 18, respectively. In the first week, the events occurred every 3 to 4 days but increased by day 19 to 4 episodes daily. Cardiac etiologies, seizures, and systemic infection were ruled out as potential causes. At this point, the diagnosis of PSH was given.

Clonidine, 0.1 mg enterally twice daily (6 mcg/kg/day), and lorazepam, 1 mg (0.03 mg/kg/dose) intravenously, were initiated as needed for autonomic episodes, but episodes continued to occur 1 to 4 times daily. Clonidine was titrated up to 0.2 mg 3 times daily (18 mcg/kg/day) but was discontinued on day 24 because of severe bradycardia between episodes. Propranolol, 5 mg enterally every 8 hours (0.4 mg/kg/day), with clonazepam, 0.5 mg enterally every 8 hours (0.04 mg/kg/day), was then initiated. Baclofen, 5 mg enterally twice daily (0.3 mg/kg/day), was added on day 28 to reduce spasticity and aid with autonomic episodes. Doses were titrated as needed to reduce symptoms and minimize toxicity. During this time, both lorazepam and later labetalol were found to be ineffective at aborting acute episodes. The autonomic storms did not abate until morphine, 2.5 mg (0.07 mg/kg/dose) intravenously as needed, was started on hospital day 35. Morphine was extremely effective at aborting episodes of PSH. During the next 2 weeks, only 4 more autonomic episodes occurred, and all were aborted with either intravenous or enteral morphine. The patient was eventually discharged on hospital day 54 to a long-term care facility receiving the following enteral medications: propranolol, 10 mg every morning, 5 mg in the afternoon, and 10 mg at night (0.7 mg/kg/day); baclofen, 20 mg every 8 hours (1.8 mg/kg/day); and clonazepam, 0.5 mg every 8 hours (0.04 mg/kg/day). Morphine, 15 mg (0.4 mg/kg/dose) enterally was given as needed for acute episodes.

This case report was exempt from Institutional Review Board approval at the University of Illinois, Chicago.

DISCUSSION

The development of PSH after brain injury is grave and leads to increased morbidity and mortality.[1,2] Excessive catecholamines lead to the characteristic signs and symptoms of PSH: tachycardia, tachypnea, hypertension, fever, diaphoresis, and dystonic posturing and rigidity.[3] The time to onset, duration, and frequency of episodes vary greatly among patients, increasing the difficulty in correctly diagnosing this condition.

Currently, there is no consensus in the diagnostic criteria or treatment approach to PSH.[3] Even the actual term used to describe this condition varies widely and includes such terminology as *PSH*, *autonomic storms*, *sympathetic storms*, *paroxysmal autonomic instability with dystonia*, *dysautonomia*, *central autonomic dysfunction*, and others. Literature does support this condition as the result of a cerebral insult, most commonly TBI.[2] Other causes include hypoxic injury, brain tumors, hydrocephalus, and stroke. It is not clear whether TBI increases the risk of PSH compared with other brain injuries or whether TBI is simply more common. Although several adult studies have demonstrated a greater incidence of PSH after TBI than after other cerebral insults,[14,15] a

study by Krach and colleagues[1] found the opposite result in pediatric patients, with a higher incidence of PSH after hypoxic brain injury (9 of 31 children; 29%) compared with TBI (20 of 166 children; 12%). Studies have additionally found that outcomes are worse in patients who develop PSH secondary to non-traumatic brain injury than they are in those with TBI.[1,15] This is consistent with our case because the patient never recovered from his vegetative state after his hypoxic insult.

The exact mechanism by which PSH occurs is unknown. Historically, it was thought to be epileptogenic in nature.[2,16] Further research found that no seizure activity is present on electroencephalogram, and PSH does not respond to anticonvulsant therapy. This is consistent with our patient, who had no seizure activity during his extensive workup. Current theories include conventional disconnection and the excitatory:inhibitory (E:I) ratio model, both of which result in excessive adrenergic activity.[16] Conventional disconnection theories, in general, describe some type of structural damage to the brain or brainstem that results in a loss of normal autonomic regulation. The E:I ratio model further suggests an allodynic tendency of PSH, which is characterized by a disproportionately large nociceptive response in the body to what should normally be non-noxious stimuli. Our patient was noted to experience some of his episodes after activities like suctioning, bathing, and repositioning, although there were not always any identifiable precipitating factors.

Once PSH is diagnosed, appropriate treatment options to both abort acute episodes and decrease the frequency and severity of future episodes should be initiated.[17,18] Many medications have been reported for treating pediatric PSH with inconsistent success in aborting or preventing episodes (see Table). As would be expected with such a rare condition, limited information is available to guide medication dosing recommendations for pediatric patients. Additionally, it would be difficult to design a study to determine the optimal medication regimen for PSH without addressing the heterogeneity of this patient population and the lack of consensus about its diagnostic criteria.

In our patient, lorazepam was found to be ineffective in aborting PSH episodes; however, morphine was extremely effective in aborting PSH, and rarely was a second dose needed for an individual episode. We used doses of morphine consistent with those for pain control (0.05–0.1 mg/kg intravenously). Morphine is commonly mentioned as a treatment option for PSH in the adult literature[17,19]; however, that use is based mainly on anecdotal reports with a wide range of doses and variable results.[20–29] Likewise, there is a paucity of evidence within the pediatric literature supporting the use of morphine. Additionally, the adult literature suggests that the efficacy of morphine for PSH is dose-dependent[16]; however, our patient did not require escalation beyond typical doses for improved efficacy.

We propose that morphine was effective because it combated the allodynic tendency of PSH.[16] Both propranolol and clonidine were found to be effective in reducing the frequency and severity of episodes, although both resulted in occasional bradycardia between episodes. Propranolol and clonidine were initiated at doses similar to those used for hypertension. Mechanistically, these agents seem ideal because they both counteract the excessive sympathetic response in PSH by reducing the outflow (clonidine) or response (propranolol) to catecholamines. Baclofen has been used in several other case reports as both an oral and intrathecal agent. Oral baclofen was found to be effective as an adjunctive agent for preventing episodes in our patient and was part of his eventual discharge regimen. Although lorazepam did not abort PSH episodes, clonazepam was helpful in the prevention of autonomic storms. Additional medications not used in our patient but used in other case reports include bromocriptine, chlorpromazine, other benzodiazepines, hydralazine, methadone, intrathecal baclofen, and hyperbaric oxygen therapy.[1,4–13]

Prompt recognition and treatment of PSH is necessary because of poor outcomes associated with this condition, especially after hypoxic brain injury. Several treatment regimens were used in our patient, with best efficacy found with morphine for acute episodes. For our patient, morphine was the only effective abortive therapy that did not produce unwanted side effects. We suggest early use of intravenous morphine as a safe and effective medication in patients whose autonomic storms do not respond to, or whose side effects limit the use of, antihypertensive agents or benzodiazepines.

Table. Summary of Reports of Pediatric Paroxysmal Sympathetic Hyperactivity (PSH)[1, 4-13]

					Treatments and Reported Effectiveness†	
Reference	**Age*(Sex)**	**Injury Type**	**Onset of PSH**	**Duration of PSH**	**Ineffective**	**Effective**
Krach et al[1] (31 patients)	9.3 ± 5.3 (NR)	Trauma (n=20) Anoxia (n=9) Other (n=2)	Within 1 mo (=28)	<6 mo (n 22)	Effect not reported: Bromocriptine, chlorpromazine, antihypertensives, muscle relaxants	
Boeve et al[4]	17 (F)	Traumatic	5 days	15 mo	Anticonvulsants, midazolam 1-3 mg IV PRN	Propranolol, 3 mg IV once; morphine, 10 mg, G-tube every 4 hr; acetaminophen, 650 mg, G-tube every 4 hr; bromocriptine, 1.25 mg, G-tube twice daily
Goh et al[5]	7 (M)	Resection of midbrain glioma	Within 1 wk	6 mo	Phenytoin, 100 mg twice daily	Diazepam, 1 mg every 6 hr; lorazepam, 1 mg IV PRN; clonidine, 100 mcg every 8 hr
Russo et al[6]	10 (F)	Traumatic	5 days	5 days	Morphine, midazolam, diazepam, 0.1 mg/kg/dose IV PRN; clonidine, 1 mcg/kg/dose IV every 6 hr	Bromocriptine, 0.025 mg/kg/dose every 12 hr
Cuny et al[7]	17 (M)	Traumatic	~60 days	48 days		Intrathecal baclofen, 96-432 mcg/day
Rodriguez et al[8]	6 (M)	Traumatic with cardiac arrest	~6 days	<76 days	Phenytoin Effect not reported: diazepam, morphine	Midazolam, baclofen
	12 (F)	Traumatic	1 day	>65 days		Diazepam, clorazepate, baclofen
Mehta et al[9]	14 (F)	Hypoxic-ischemic	1 wk	8 wk	Anticonvulsants, atenolol, clonidine, hydralazine, morphine, fentanyl, methadone, bromocriptine, intrathecal baclofen	Baclofen pump
Woo et al[10]	12 (M)	Traumatic	1 day	3 wk (spastic at 3 mo)		Midazolam, morphine
Singh et al[11]	1 (F)	Intracranial tuberculoma	Not stated	>1 mo		Benzodiazepines, β-blockers, clonidine
Lv et al[12]	8 (M)	Traumatic	10 days	~40 days	Midazolam, propranolol, bromocriptine	Morphine, hyperbaric oxygen therapy
Deepika et al[13]	6 (F)	Right middle cerebral artery infarction with Moyamoya	3 days	Until death at 28 days post-infarction	Dexmedetomidine, 1 mcg/kg/hr IV; metoprolol, 50 mg/day; clonidine, 0.1 mg/day	

IV, intravenous; NR, not reported; PRN, as needed

* age in years

† Doses and route included when reported.

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Abbreviations E:I, excitatory:inhibitory; IV, intravenous; PRN, as needed; PSH, paroxysmal sympathetic hyperactivity; TBI, traumatic brain injury

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REFERENCES

1. Krach LE, Kriel RL, Morris WF, et al. Central autonomic dysfunction following acquired brain injury in children. *Neurorehabil Neural Repair.* 1997;11(1):41-45.
2. Perkes I, Baguley IJ, Nott MT, Menon DK. A review of paroxysmal sympathetic hyperactivity after acquired brain injury. *Ann Neurol.* 2010;68(2):126-135.
3. Perkes IE, Menon DK, Nott MT, Baguley IJ. Paroxysmal sympathetic hyperactivity after acquired brain injury: a review of diagnostic criteria. *Brain Injury.* 2011;25(10):925-932.
4. Boeve BF, Wijdicks EFM, Benarroch EE, Schmidt KD. Paroxysmal sympathetic storms ("diencephalic seizures") after severe diffuse axonal head injury. *Mayo Clin Proc.* 1998;73(2):148-152.
5. Goh KYC, Conway EJ, DaRosso RC, et al. Sympathetic storms in a child with a midbrain glioma: a variant of diencephalic seizures. *Pediatr Neurol.* 1999;21(4):724-744.
6. Russo RN, O'Flaherty S. Bromocriptine for the management of autonomic dysfunction after severe traumatic brain injury. *J Paediatr Child Health.* 2000;36(3):283-285.
7. Cuny E, Richer E, Castel JP. Dysautonomia syndrome in the acute recovery phase after traumatic brain injury: relief with intrathecal baclofen therapy. *Brain Injury.* 2001;15(10):917-925.
8. Rodríguez N, Febrer A, Meléndez M. Autonomic dysfunction in children with traumatic brain injury [in Spanish]. *Rev Neurol.* 2006;43(3):143-146.
9. Mehta NM, Bechard LJ, Leavitt K, Duggan C. Severe weight loss and hypermetabolic paroxysmal dysautonomia following hypoxic ischemic brain injury: the role of indirect calorimetry in the intensive care unit. *J Parenter Enteral Nutr.* 2008;32(3):281-284.
10. Woo HJ, Park SH, Hwang SK. A unique pattern of intracranial pressure in a patient with traumatic paroxysmal sympathetic storm. *Pediatric Neurosurg.* 2010;46(4):299-302.
11. Singh DK, Singh N. Paroxysmal autonomic instability with dystonia in a child: rare manifestation of an interpenduncular tuberculoma. *Pediatr Neurosurg.* 2011;47(4):275-278.
12. Lv LQ, Hou LJ, Yu MK, et al. Hyperbaric oxygen therapy in the management of paroxysmal sympathetic hyperactivity after severe traumatic brain injury: a report of 6 cases. *Arch Phys Med Rehabil.* 2011;92(9):1515-1518.
13. Deepika A, Reddy M, Shukla D. Paroxysmal sympathetic hyperactivity in a child with Moyamoya disease. *J Neurosurg Anesthesiol.* 2014;26(1):87-88.
14. Rabinstein AA. Paroxysmal sympathetic hyperactivity in the neurological intensive care unit. *Neurol Research.* 2007;29(7):680-682.
15. Pignolo L, Rogano S, Quintieri M, et al. Decreasing incidence of paroxysmal sympathetic hyperactivity syndrome in the vegetative state. *J Rehabil Med.* 2012;44(6):502-504.
16. Baguley IJ, Heriseanu RE, Cameron ID, et al. A critical review of the pathophysiology of dysautonomia following traumatic brain injury. *Neurocrit Care.* 2008;8(2):293-300.
17. Rabinstein AA, Benarroch EE. Treatment of paroxysmal sympathetic hyperactivity. *Curr Treatment Options in Neurol.* 2008;10(2):151-157.
18. Baguley IJ, Cameron ID, Green AM, et al. Pharmacological management of dysautonomia following traumatic brain injury. *Brain Injury.* 2004;18(5):409-417.
19. Hinson HE, Sheth KN. Manifestations of the hyperadrenergic state after acute brain injury. *Curr Opin Crit Care.* 2012;18(2):139-145.

20. Baguley IJ, Heriseanu RE, Gurka JA, et al. Gabapentin in the management of dysautonomia following severe traumatic brain injury: a case series. *J Neurol Neurosurg Psychiatry.* 2007;78(5):539-541.
21. Bower RS, Sunnarborg R, Rabinstein AA, Wijdicks EF. Paroxysmal sympathetic hyperactivity after traumatic brain injury. *Neurocrit Care.* 2010;13(2):233-234.
22. Bullard DE. Diencephalic seizures: responsiveness to bromocriptine and morphine. *Ann Neurol.* 1987;21(6):609-611.
23. Diamond AL, Callison RC, Shokri J, et al. Paroxysmal sympathetic storm. *Neurocrit Care.* 2005;2(3):288-291.
24. Goddeau RP Jr, Silverman SB, Sims JR. Dexmedetomidine for the treatment of paroxysmal autonomic instability with dystonia. *Neurocrit Care.* 2007;7(3):217-220.
25. Huang P, Lin W, Huang P, Khor GT. Susceptibility weighted imaging in a patient with paroxysmal sympathetic storms. *J Neurol.* 2009;256(2):276-278.
26. Ko S, Kim CK, Lee S, et al. Morphine-sensitive paroxysmal sympathetic storm in pontine intracerebral hemorrhage. *Neurologist.* 2010;16(6):384-385.
27. Levy ER, McVeigh U, Ramsay AM. Paroxysmal sympathetic hyperactivity (sympathetic storm) in a patient with permanent vegetative state. *J Palliat Med.* 2011;14(12):1355-1357.
28. Oh SJ, Hong YK, Song E. Paroxysmal autonomic dysregulation with fever that was controlled by propranolol in a brain neoplasm patient. *Korean J Internal Med.* 2007;22(1):51-54.
29. Srinivasan S, Lim CCT, Thirugnanam U. Paroxysmal autonomic instability with dystonia. *Clin Auton Res.* 2007;17(6):378-381.