EDITORIAL

Paroxysmal Sympathetic Hyperactivity after Traumatic Brain Injury: Current Understanding and Therapeutic Options

Prashant Nasa[1], Nimisha A Majeed[2], Deven Juneja[3]

Keywords: Acute brain injury, Autonomic dysfunction, Autonomic instability, Autonomic storm, Brain injuries traumatic, Paroxysmal sympathetic hyperactivity.

Indian Journal of Critical Care Medicine (2024): 10.5005/jp-journals-10071-24647

Paroxysmal sympathetic hyperactivity (PSH), as the name suggests, is an episodic sympathetic upsurge after a severe brain injury and is characterized by a paroxysm of hyperthermia, hypertension, tachycardia, tachypnea, diaphoresis, and posturing such as dystonia, hypertonia, or spasticity.[1] Previously, the condition was referred to by many alternative names, such as dysautonomia, sympathetic storms, and autonomic storms. The nomenclature PSH was adopted by an international expert group that also provided a consensus definition and diagnostic criteria for clinical and research purposes using a Delphi approach.[2] The diagnosis is mainly clinical in patients with risk factors, and no specific laboratory test is required. Tachycardia is the most common sign, but not all signs may always be present, with posturing being absent in half of the cases. Posturing or dystonia is observed only in the most severe cases and can mimic tonic-clonic seizures. The absence of parasympathetic signs such as bradycardia or hypotension is characteristic.[1,2]

Epidemiology

Paroxysmal sympathetic hyperactivity has been described with many conditions, most commonly in patients with severe traumatic brain injury (TBI) but can also occur with non-traumatic brain injuries such as post-cardiac arrest hypoxic-ischemic encephalopathy, and cerebrovascular accident (mostly intracranial hemorrhage).[3–5] The reported incidence of PSH varies between 10 and 30% in patients with severe TBI and depends on the clinical setting (Intensive Care Unit vs Rehabilitation Unit), the diagnostic criteria applied, patient population studied and timing of assessment. Although the incidence is higher in patients with severe TBI, the severity of brain injury does not correlate with the risk of PSH.[6] The incidence is higher in young patients compared to older adults and in patients with diffuse axonal injury.

Pathophysiology

The pathophysiology of PSH is incompletely understood, and the current hypothesis is a disconnection theory between excitatory and inhibitory sympathetic center. Brain injury causes a disconnection between sympathetic inhibitory areas in the cortex (dorsolateral prefrontal cortex, amygdala, and basal ganglia) and lower sympathetic centers in the diencephalon (mainly the hypothalamus), brainstem, and spinal cord. This leads to excessive sympathetic surge after internal or external triggers. As per another hypothesis, disconnection is a two-stage process with the development of excitatory spinal circuits at the spinal level due to loss of descending inhibition from the brainstem. Non-noxious stimuli elicit a maladaptive spinal cord response with motor or sympathetic outflow, which is misinterpreted as a noxious stimulus centrally.[5,7]

[1]Department of Critical Care Medicine, NMC Specialty Hospital; Department of Internal Medicine, College of Medicine and Health Sciences, Abu Dhabi, United Arab Emirates

[2]Department of Critical Care Medicine, NMC Specialty Hospital, Abu Dhabi, United Arab Emirates

[3]Department of Critical Care Medicine, European Society of Intensive Care Medicine (ESICM), Brussels, Belgium; Max Super Specialty Hospital, Saket, New Delhi, India

Corresponding Author: Prashant Nasa, Department of Critical Care Medicine, NMC Specialty Hospital, Abu Dhabi, United Arab Emirates, Phone: +971 42122255, e-mail: dr.prashantnasa@hotmail.com

How to cite this article: Nasa P, Majeed NA, Juneja D. Paroxysmal Sympathetic Hyperactivity after Traumatic Brain Injury: Current Understanding and Therapeutic Options. Indian J Crit Care Med 2024;28(2):97–99.

Source of support: Nil

Conflict of interest: None

Diagnosis

The diagnosis of PSH is mainly clinical. The consensus diagnostic criteria proposed by the international panel of experts include a combination of clinical feature score (CFS) and diagnosis likelihood tool (DLT) to predict the likelihood of presence of PSH (Table 1).[2] The tool is validated for adults and pediatric patients.[8] However, it is imperative to exclude differential diagnoses, such as sepsis, malignant hyperthermia, malignant neuroleptic syndrome, serotonin syndrome, drug withdrawal, and endocrine emergencies such as thyroid storm, before making a diagnosis of PSH. The CFS can also be used to monitor the severity of episodes and symptom progression with the exclusion of other confounding conditions, and helps in confirming the diagnosis.

The external triggers for an episode include tracheal suctioning, loud noises, patient positioning, and urinary retention, which are usually minuscule and inconsistent, and sometimes, paroxysms can occur without an apparent trigger. The duration of an episode depends on its severity, and efficacy and timing of the treatment; an untreated episode may last between 20 and 30 minutes.[9]

Table 1: Diagnosis of paroxysmal sympathetic hyperactivity

Clinical feature scale (CFS)				
Variables	0	1	2	3
Heart rate (beats/min)	<100	100–119	120–139	≥140
Respiratory rate (breaths/min)	<18	18–23	24–29	≥30
Systolic BP (mm Hg)	<140	140–159	160–179	≥180
Temperature (°C)	<37	37–37.9	38–38.9	≥39
Sweating	None	Mild (moist skin)	Moderate (beads of sweat)	Severe (profuse generalized)
Posture	None	Mild (increased tone, not requiring treatment)	Moderate (increased tone requiring treatment)	Severe (very increased tone refractory to treatment)
Diagnosis likelihood tool (DLT) (1 score for each positive variable)				
Clinical features occur simultaneously				
Episodes are paroxysmal in nature				
Over-reactivity to normally nonpainful stimuli				
Features persist ≥3 consecutive days				
Features persist ≥2 weeks post-brain injury				
Features persist despite treatment of differential diagnoses				
Medication administered to decrease sympathetic features				
≥2 episodes daily				
Absence of parasympathetic features during episodes				
Absence of other presumed cause of features				
Antecedent acquired brain injury				
Diagnosis: Add scores of CFS and DLT				
<8				PSH unlikely
8–16				PSH possible, monitor CFS daily
≥17				PSH probable
Use maximal score for diagnosis				

Source: Rabinstein AA, Dolce G, Hendricks HT; Consensus Working Group. Paroxysmal sympathetic hyperactivity after acquired brain injury: Consensus on conceptual definition, nomenclature, and diagnostic criteria. J Neurotrauma 2014;31(17):1515–1520. DOI: 10.1089/neu.2013.3301.

Prognosis

Paroxysmal sympathetic hyperactivity is more likely to be associated with more diffuse brain injury, which has an inherent association with worse outcomes. The syndrome can manifest during the entire course of the brain injury, i.e., from the critical initial phase to rehabilitation. However, the average duration of symptoms reported is between 18 days and a year.

In many case series, PSH in patients with TBI was associated with worse long-term outcomes. This includes longer hospital stays, higher ventilator dependence, need for tracheostomy, and risk of infectious complications.[10,11] Severe and more frequent episodes correlated with worse outcomes. The risk of the unopposed sympathetic surge is end-organ damage, especially intracerebral hemorrhage. The delayed complications include weight loss due to metabolic hyperactivity, joint heterotopic ossification, muscle contractures (due to dystonia), and poor functional outcomes.

Treatment

The optimum management for PSH still needs to be established. The treatment is mainly supportive and includes a combination of pharmacotherapy to abort and prevent the episodes of PSH. The goals of the treatment are to prevent the recurrence, frequency, and severity of episodes. The drugs target three primary pathophysiological mechanisms of PSH: (1) stimulation trigger of PSH; (2) afferent sympathetic surge; and (3) effect on sympathetic hyperactivity on target end-organs.

Several pharmacological agents acting at different sites have been investigated, but the management is yet to be standardized due to a lack of enough evidence.[7] Common pharmacological agents used are beta-blockers, alpha-2 agonists, bromocriptine, gabapentin, baclofen, and benzodiazepines. Pharmacotherapy can be abortive, preventive, or both.

Drugs like morphine are predominantly abortive, while drugs such as gabapentin, bromocriptine, or beta-blockers are preventive only. Benzodiazepines, propofol, clonidine, and dexmedetomidine have dual action. The treatment is usually multi-modal and needs a combination of pharmacotherapeutic agents to abort an episode and prevent its recurrence, supportive measures to control the symptom, and removal of an offending stimulus. Paroxysmal sympathetic hyperactivity being a heterogenous pathophysiological syndrome, the therapeutic options depend on the predominant phenotype in a particular patient and the side effects of an individual drug. However, large prospective studies comparing different drugs for effectiveness and side effects are lacking.[7,12]

Reducing and Removing External Triggers

It can usually be difficult, especially since most triggers are part of the routine care of these patients. Sedation is often required and effective but has its limitations.

Control of Hyperpyrexia

The fever control often requires antipyretics. However, fever is usually refractory to antipyretics and needs abortive medications to control the episode.

Other Supportive Care

Frequent episodes need correction of electrolytes, dehydration, and nutrition support.

Gabapentin (gamma-aminobutyric acid) acts on the alpha-2 delta subunit of presynaptic voltage-gated Ca^{2+} channels in the brain and spinal cord. Gabapentin is effective in recovering the descending cortical inhibitory control and afferent feedback at the level of the brain and spinal cord. In the current issue of this journal, Singh et al. evaluated the effects of gabapentin in preventing PSH and secondary worsening of patients with TBI through a single-center prospective placebo-controlled study. The study found that gabapentin was effective in reducing the episodes of PSH, need for sedation, and better neurological outcomes at day 30 and day 90.[13]

Conclusion

Paroxysmal sympathetic hyperactivity is a common complication associated with severe brain injury, especially in trauma patients, and may worsen patient outcomes. Large-scale prospective research is required on the epidemiology of PSH, and the effectiveness of drugs for its prevention and treatment.

Orcid

Prashant Nasa https://orcid.org/0000-0003-1948-4060
Nimisha A Majeed https://orcid.org/0000-0002-9468-6626
Deven Juneja https://orcid.org/0000-0002-8841-5678

References

1. Hughes JD, Rabinstein AA. Early diagnosis of paroxysmal sympathetic hyperactivity in the ICU. Neurocritical Care 2014;20(3):454–459. DOI: 10.1007/s12028-013-9877-3.
2. Baguley IJ, Perkes IE, Fernandez-Ortega JF, Rabinstein AA, Dolce G, Hendricks HT, et al. Paroxysmal sympathetic hyperactivity after acquired brain injury: Consensus on conceptual definition, nomenclature, and diagnostic criteria. J Neurotrauma 2014;31(17): 1515–1520. DOI: 10.1089/neu.2013.3301.
3. Nasa P. Outcome of hemorrhagic stroke: Host immune response can be a prediction tool! Indian J Crit Care Med 2022;26(1):2–4. DOI: 10.5005/jp-journals-10071-24095.
4. 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. DOI: 10.1002/ana.22066.
5. Jafari AA, Shah M, Mirmoeeni S, Hassani MS, Nazari S, Fielder T, et al. Paroxysmal sympathetic hyperactivity during traumatic brain injury. Clin Neurol Neurosurg 2022;212:107081. DOI: 10.1016/j.clineuro.2021.107081.
6. Meyfroidt G, Baguley IJ, Menon DK. Paroxysmal sympathetic hyperactivity: The storm after acute brain injury. Lancet Neurol 2017;16(9):721–729. DOI: 10.1016/S1474-4422(17)30259-4.
7. Xu SY, Zhang Q, Li CX. Paroxysmal sympathetic hyperactivity after acquired brain injury: An integrative review of diagnostic and management challenges. Neurol Ther 2023. DOI: 10.1007/s40120-023-00561-x.
8. Alofisan TO, Algarni YA, Alharfi IM, Miller MR, Charyk Stewart T, Fraser DD, et al. Paroxysmal sympathetic hyperactivity after severe traumatic brain injury in children: Prevalence, risk factors, and outcome. Pediatr Crit Care Med 2019;20(3):252–258. DOI: 10.1097/PCC.0000000000001811.
9. Fernandez-Ortega JF, Baguley IJ, Gates TA, Garcia-Caballero M, Quesada-Garcia JG, Prieto-Palomino MA. Catecholamines and paroxysmal sympathetic hyperactivity after traumatic brain injury. J Neurotrauma 2017;34(1):109–114. DOI: 10.1089/neu.2015.4364.
10. Mathew MJ, Deepika A, Shukla D, Devi BI, Ramesh VJ. Paroxysmal sympathetic hyperactivity in severe traumatic brain injury. Acta Neurochir (Wien) 2016;158(11):2047–2052. DOI: 10.1007/s00701-016-2934-x.
11. Lv LQ, Hou LJ, Yu MK, Qi XQ, Chen HR, Chen JX, et al. Prognostic influence and magnetic resonance imaging findings in paroxysmal sympathetic hyperactivity after severe traumatic brain injury. J Neurotrauma 2010;27(11):1945–1950. DOI: 10.1089/neu.2010.1391.
12. Nguembu S, Meloni M, Endalle G, Dokponou H, Dada OE, Senyuy WP, et al. Paroxysmal sympathetic hyperactivity in moderate-to-severe traumatic brain injury and the role of beta-blockers: A scoping review. Emerg Med Int 2021;2021:5589239. DOI: 10.1155/2021/5589239.
13. Singh R, Ambasta S, Bais PS, Azim A, Kumar S, Upreti B, et al. Role of gabapentin in traumatic brain injury: A prospective comparative study. Indian J Crit Care Med 2024;28(2):120–125.