

CASE REPORT

Open Access



Paroxysmal sympathetic hyperactivity following acute diffuse brain swelling due to traumatic brain injury: a case report with good clinical outcome

Kyohei Sakai^{1,2*}, Takehiro Kitagawa^{1,2†}, Kohei Suzuki², Keita Toh² and Junkoh Yamamoto²

Abstract

Background: Paroxysmal sympathetic hyperactivity (PSH) may occur after acquired brain injury. The clinical presentation of PSH results from increased sympathetic overdrive, including transient paroxysms of tachycardia, hypertension, hyperventilation, hyperthermia, dystonic posturing, and excessive sweating. The exact pathophysiology of PSH, however, remains unclear, and no definitive treatment is available. Herein, the authors report a case of PSH in a male patient who experienced acute brain swelling after acquired head injury, for which a good clinical outcome was achieved due to multimodal treatment. The ensuing discussion also addresses the pathophysiology of PSH.

Case presentation: An 18-year-old man was transported to the authors' hospital after experiencing a traumatic brain injury. On admission, computed tomography revealed cerebral herniation due to diffuse brain edema in the left parietal lobe. Emergency decompressive craniotomy and internal decompression were performed. After surgery, anti-edema therapy (glycerol and mannitol) was continued. Ten days postoperatively, PSH was diagnosed in accordance with the PSH assessment score (20 points). Vecuronium, fentanyl, morphine, propofol, dexmedetomidine, and a calcium channel blocker were administered; however, the drug effect was insufficient. Thirty-two days postsurgery, the patient gradually recovered from the adrenergic symptoms of PSH, and head computed tomography performed 32 days after surgery revealed improvement in diffuse brain edema. Ultimately, the patient fully recovered and lived independently at home.

Conclusions: Considering the pathophysiology of PSH, cerebral contusion, acute brain swelling, and secondary mechanisms of brain injury may trigger sympathetic nerve-enhancing regions and cause hyperexcitation of the sympathetic nervous system, resulting in PSH. The outcome of the present case demonstrates that PSH can be reversed if it is identified early and before it becomes irreversible, that is, post the development of hypoxic encephalopathy or widespread brain damage. Appropriate management, including decompression craniotomy for brain swelling and multidisciplinary treatment, leads to good clinical outcomes.

Keywords: Paroxysmal sympathetic hyperactivity, Acute brain swelling, Insular cortex

Background

Paroxysmal sympathetic hyperactivity (PSH) may occur after acquired brain injury. The clinical presentation of PSH is due to increased sympathetic overdrive and includes transient paroxysms of tachycardia, hypertension, hyperventilation, hyperthermia, and excessive

*Correspondence: kyoheisakai1226@gmail.com

†Kyohei Sakai and Takehiro Kitagawa have contributed equally to this work

¹ Department of Neurosurgery, Kitakyushu Municipal Yahata Hospital, 2-6-2 Ogura, Yahata-Higashi, Kitakyushu, Fukuoka 805-8534, Japan
Full list of author information is available at the end of the article

sweating. Excessive motor tone may result in dystonic posturing [1]. Currently, the most widely accepted diagnostic criteria for PSH are those proposed by Baguley et al. (Table 1) [1].

Recently, the clinical and diagnostic features of PSH in patients experiencing traumatic brain injury (TBI) have reached broad clinical consensus in many neurology departments. These advances in understanding should provide a unanimous foundation for systematic research investigating this clinical syndrome and its management. Clinically, significant attention has been devoted to the definition and diagnostic criteria, epidemiology and pathophysiology, symptomatic treatment, and prevention and control of secondary brain injury in patients

with TBI. The primary goals of treatment include removing any eliciting stimuli, controlling excessive sympathetic hyperactivity, and preventing damage to peripheral organ systems [2, 3]. Delayed recognition, leading to unnecessary workup and medications, can further prolong hospitalization, with potentially harmful results for patients. Uncontrolled symptoms can lead to secondary brain injury from hypertension, hyperthermia, cardiac damage, and even death [4, 5]. However, the exact pathophysiology of PSH remains unclear, and there is no definitive treatment; moreover, perioperative management is difficult and the prognosis is poor [6]. Herein, we report a case of PSH after acute brain swelling due to acquired head injury, for which a good clinical outcome

Table 1 Paroxysmal sympathetic hyperactivity assessment

Clinical Feature Scale (CFS)					
	0	1	2	3	Score
Heart rate	<100	100-119	120-139	≥ 140	
Respiratory rate	<18	18-23	24-29	≥ 30	
Systolic blood pressure	<140	140-159	160-179	≥ 180	
Temperature	<37	37-37.9	38-38.9	≥ 39.0	
Sweating	Nil	Mild	Moderate	Severe	
Posturing during episodes	Nil	Mild	Moderate	Severe	
				CFS subtotal	
Severity of clinical features			Nil	0	
			Mild	1-6	
			Moderate	7-12	
			Severe	>12	
Diagnosis Likelihood (DLT)					
Clinical features occur simultaneously					
Episodes are paroxysmal in nature					
Sympathetic over-reactivity to normally non-painful stimuli					
Features persist >3 consecutive days					
Features persist >2 weeks post brain injury					
Medication administered to decrease sympathetic features					
≥ 2 episodes daily					
Absence of parasympathetic features					
Absence of other presumed cause of features					
Antecedent acquired brain injury					
				DLT subtotal	
Combined total (CFS+DLT)					
PSH diagnostic likelihood			Unlikely	<8	
			Possible	8-16	
			Probable	>16	

was achieved due to multimodal treatment. The ensuing discussion also addresses the pathophysiology of PSH.

Case presentation

An 18-year-old man was transported to the authors' hospital with altered levels of consciousness after experiencing TBI, having fallen from a height of 9 m. On admission, he had a Glasgow Coma Scale (GCS) score of 10 (E3V2M5), motor strength and tone were normal, and pupils were equal in size. Brain computed tomography (CT) on admission revealed left temporal lobe contusion and diffuse subarachnoid hemorrhage (Fig. 1). Whole-body CT revealed multiple fractures (right clavicle and femur), multiple lung contusions, and a left pneumothorax. The patient required mechanical ventilation due to a reduced level of consciousness, while brain edema was managed conservatively with anti-cerebral edema drugs (glycerol 400 ml/24 h and mannitol 600 ml/24 h). An external fixation of open fracture of the right femur was performed. Four hours after the injury, the patient's pupils became unequal in size (right, 3 mm; left, 6 mm), and head CT revealed cerebral herniation due to diffuse brain edema in the left parietal lobe. Emergency decompressive craniotomy and internal decompression were performed. Intraoperatively, a dural incision was made as large as possible within the craniotomy, and the brain parenchyma bulged beyond the dural margin. The soft membrane vessels on the surface of the left parietal lobe were markedly dilated, suggesting impaired reflux due to increased cerebral pressure. Approximately two-thirds of the brain parenchyma, which was bulging

extradurally, was resected. After the operation, anti-edema therapy (glycerol 400 ml/24 h and mannitol 600 ml/24 h) was continued. Two days after the operation, the patient developed high temperature and extensor posturing; accordingly, vecuronium (50 mg/24 h), fentanyl (0.4 mg/24 h), levetiracetam (1000 mg/24 h), and intravenous injections of propofol were initiated. However, atelectasis recurred, and tracheotomy was performed 4 days after the initial operation. Ten days after the operation, the patient was awake. He also exhibited high blood pressure induced by pain and stimulation, tachycardia, tachypnea, high fever, and diaphoresis. PSH was diagnosed in accordance with a PSH assessment score of 20 points [1]. Investigations for sepsis and non-convulsive epileptic seizures were negative. Morphine (150 mg/48 h), dexmedetomidine (200 µg/24 h), benzodiazepine (midazolam) (40 mg/24 h), and a calcium channel blocker (nicardipine) (96 mg/24 h) were administered; nevertheless, his adrenergic symptoms persisted, suggesting that drug effects were insufficient. He was administered sufficient hydration to compensate for the increased insensible losses caused by excessive diaphoresis and hyperthermia management with acetaminophen, diclofenac sodium, and external cooling measures. Fourteen days after surgery, the patient was extubated. Thirty-two days postsurgery, the patient eventually recovered from the adrenergic symptoms of PSH. Additionally, the patient's communication gradually improved. Head CT performed 32 days after surgery revealed an improvement of diffuse brain edema. Forty-three days after the operation, cranioplasty was performed, and the

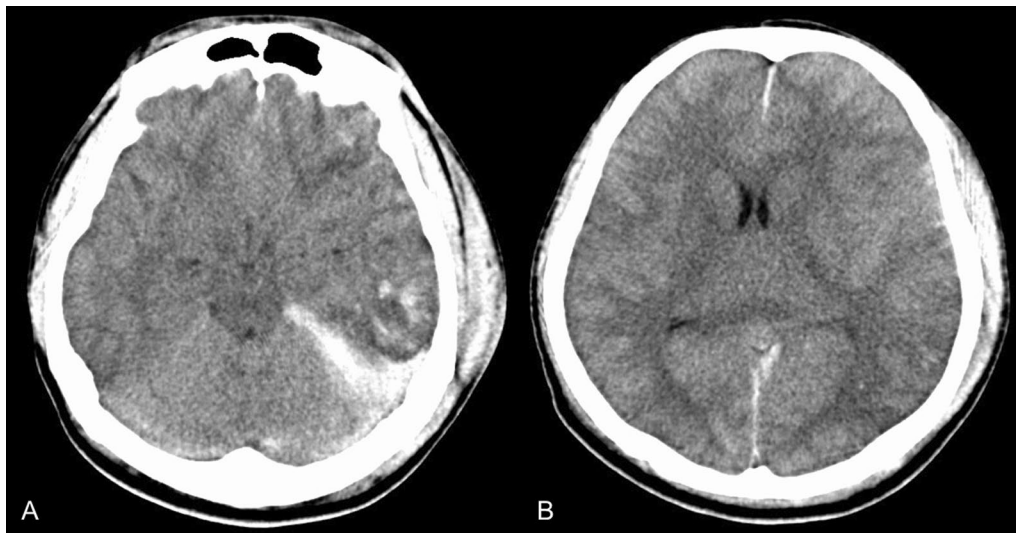


Fig. 1 Head computed tomography on admission revealing left temporal lobe contusion and diffuse subarachnoid hemorrhage

tracheal cannula was removed 50 days after decompressive craniotomy. The patient fully recovered and lived independently at home (Fig. 2).

Discussion

PSH, defined as a state of sympathetic hyperactivity consisting of periodic episodes of increased heart rate, blood pressure, sweating, hyperthermia, and motor posturing, can develop after severe acquired brain injury. Recently, the PSH assessment measure proposed by Baguley et al. has been used for the early diagnosis of PSH (Table 1) [1, 7]. In our patient, the PSH assessment score was 20 points.

Patients who experience PSH are typically young [7, 8]. The most common underlying cause is head injury (79.4%); approximately 10% of patients with severe head injury develop PSH [6, 8]. In particular, it has been reported that the frequency of PSH is high in patients who experience diffuse axonal injury and deep cerebral lesions [6]. Other causes of PSH include hypoxic encephalopathy (9.7%), which often has a poor prognosis, stroke (5.4%), hydrocephalus (2.6%), brain tumor, central nervous system infections, and hypoglycemia [8]. The paroxysms usually begin 5–7 days after the injury, although they may start earlier. The duration of the PSH phase is variable, ranging from <2 weeks to several months [9]. PSH prolongs intensive care unit stay, coma duration,

and the time on mechanical ventilation [6]. Our patient was a young man who developed acute brain swelling after experiencing a severe head injury that required craniotomy decompression. The patient was diagnosed with PSH 10 days after experiencing brain injury, and PSH symptoms persisted for 21 days. Sepsis, non-convulsive epileptic seizures, and hypoxia were considered as the differential diagnosis; however, the results of various tests were negative. The patient’s outcome was favorable following active whole-body management. PSH symptoms gradually improved and resolved immediately after the brain swelling had improved.

While the exact pathophysiology of PSH remains unclear, three mechanisms have been proposed. First, the disconnection theory suggests that the sympathetic nerve centers in the hypothalamus and brainstem are separated from the control of the higher cerebral cortex, resulting in sympathetic excitement [8, 10]. In the second, recently proposed model, the excitatory–inhibitory ratio model, proposes that disconnection of descending inhibition produces maladaptive dendritic arborization and spinal-circuit excitation, with non-noxious stimuli triggering increased motor and sympathetic output (spinally) and potentially becoming perceived as noxious (centrally) [11]. The third theory suggests that the sympathetic nervous system causes hyperexcitability due to disorders in the insula, which has been reported to be involved in

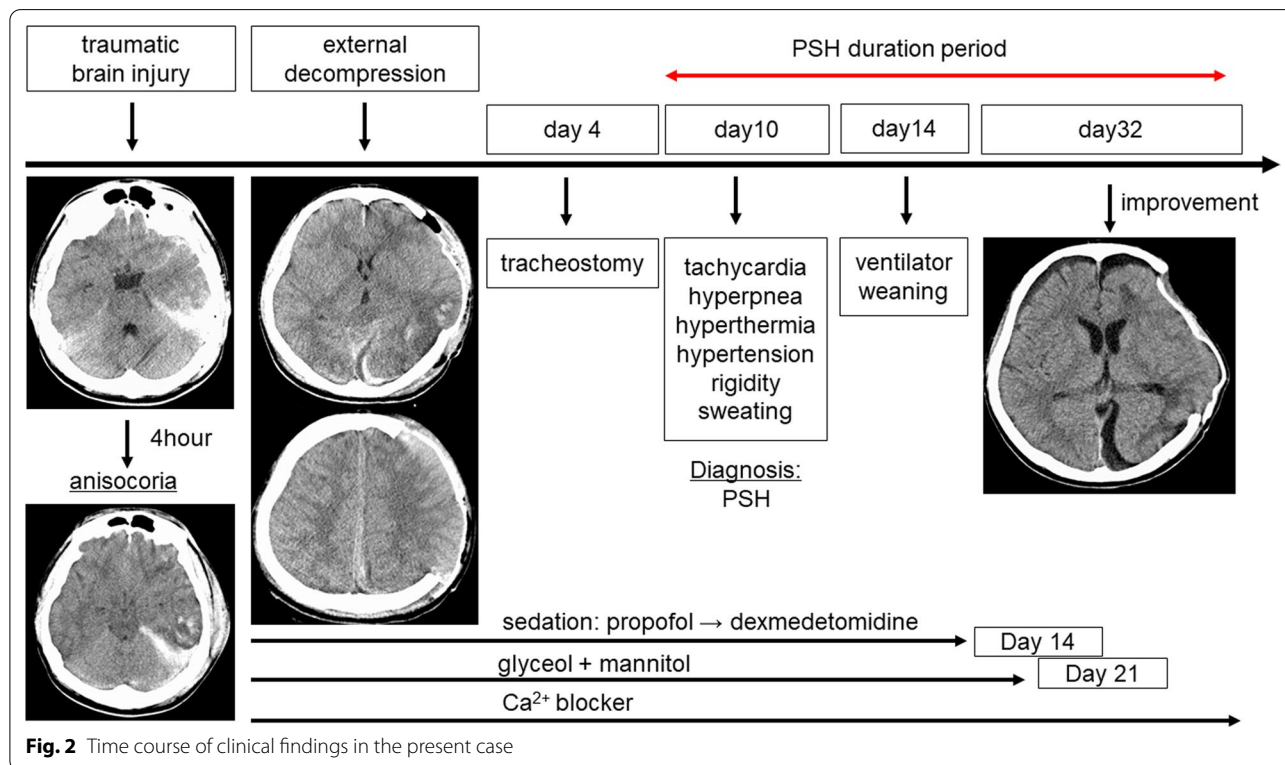


Fig. 2 Time course of clinical findings in the present case

the sympathetic tone and may be linked to sympathetic hyperexcitation [12]. Sympathetic nervous hyperexcitation causes excess catecholamine release, leading to PSH. The posterior part of the right insula, bilateral supra-marginal gyrus, right amygdala, anterior part of the left insula, and mid-cingulate gyrus have been reported to enhance the sympathetic nervous system [13]. In addition, patients with PSH have been reported to exhibit high plasma catecholamine levels, making the measurement of blood catecholamine levels during PSH attacks particularly useful [14].

In the present case, cerebral contusion damaged the left anterior insula and supra-marginal gyrus, with subsequent generalized swelling of the brain. This case indicates that primary brain contusion, extensive brain swelling, and secondary brain injury may trigger dysfunction of the cerebral sympathetic nervous system. The similarity in the course of PSH to that of Takotsubo cardiomyopathy and neuro-pulmonary edema observed after stroke supports this mechanism [13]. From that report and the current case, brain contusion following head trauma, acute brain swelling, cerebral ischemia, and subsequent release of excitatory amino acids at the cellular level may contribute to the development of PSH. We speculate that secondary brain injury due to factors, such as the production of inflammatory cytokines and reactive oxygen species, hyperthermia, hypoxemia, and the deterioration of general condition, may be involved in the pathophysiology of PSH.

In clinical practice, most patients with PSH require multiple drugs with complementary roles. However, the selection of drug combinations is typically based on local practices rather than objective evidence [11]. The management of PSH requires a combination of pharmacological and non-pharmacological treatment modalities. Since the etiology of the disease is not clearly understood, therapy has focused on symptom control [15, 16]. Opioids (morphine and fentanyl), intravenous anesthetics (propofol), gabapentin, benzodiazepines (diazepam, midazolam, and clonazepam), alfa-2 agonists, and beta-adrenergic blockers have been used [11]. The mechanisms by which these agents improve the symptoms of PSH remain speculative; however, a combination of medications from different classes appears to be the most effective approach in managing PSH symptoms. Optimizing outcomes with these medications and minimizing side effects, such as sedation, is the goal but can be a challenge. Ideally, the appropriate approach to preventing side effects is by using short-acting medications, choosing the appropriate regimen, and avoiding medications that fail to control symptoms. The pharmacological management of PSH focuses on three treatment approaches: symptom abortion, prevention of symptoms, and refractory treatment.

Symptom-abortive medications are used to control discrete breakthrough episodes. These medications have a rapid onset of action with a short half-life. The targets of abortive medications usually depend on the predominant symptoms: treating hyperthermia with antipyretics, agitation with sedation, and hypertension with antihypertensive agents [15, 16].

Our case highlights the role of multidisciplinary systemic management in preventing mortality and long-term morbidity. We demonstrated that PSH can be reversed if it is identified early before it becomes irreversible, that is, post the development of hypoxic encephalopathy or widespread brain damage. It is important to actively prevent secondary brain injury through body temperature and blood pressure management, dehydration prevention, nutritional management, and rehabilitation.

A limitation of this case was that we could not measure serum catecholamine levels or monitor intracranial pressure and perform magnetic resonance imaging. As such, it was difficult to provide an objective evidence of symptomatic nerve stimulation and objectively attribute reduced intracranial pressure to our management efforts, identifying detailed areas of brain damage. Cranial CT has limitations in detecting non-hemorrhagic lesions and those located in the posterior cranial fossa. Moreover, various authors have reported that magnetic resonance imaging is more sensitive than CT in diagnosing the anatomical sequelae of TBI, especially in detecting non-hemorrhagic lesions and those located in the corpus callosum, deep nuclei, and brain stem [17–19].

Conclusions

Cerebral contusion due to head injury, acute brain swelling, and secondary mechanisms of brain injury may trigger sympathetic nerve-enhancing regions and cause hyperexcitation of the sympathetic nervous system, resulting in PSH. We believe that PSH is reversible if appropriate interventions are implemented before it becomes irreversible. Some features identified from evidence-based clinical practice will provide predictors for the early identification of PSH in TBI patients. Moreover, some risk factors, such as age, early fever, the GCS score, and the use of tracheostomy, have been reported to be associated with the development of PSH. In the future, rigorous investigations and prospective studies are needed to accumulate reliable data, for example, to establish whether individual management modulates the relationship between the severity of PSH and long-term neurological outcomes in TBI patients and to stratify complications caused by PSH as an entity or PSH associated with TBI. Appropriate management, including decompression craniotomy for brain swelling and

multidisciplinary treatment, may result in good clinical outcomes.

Abbreviations

CT: Computed tomography; GCS: Glasgow Coma Scale; PSH: Paroxysmal sympathetic hyperactivity; TBI: Traumatic brain injury.

Acknowledgements

Not applicable.

Authors' contributions

KS was directly involved in the patient's diagnosis and care and acquired the data and drafted the manuscript. TK was involved in the patient's diagnosis, surgery, and patient care and revised and reviewed the manuscript. KS was involved in the patient's diagnosis, surgery, and care. KT was involved in the patient's diagnosis, surgery, and care. JY was involved in the patient's diagnosis and surgery and revised the manuscript draft. All authors read and approved the final manuscript.

Funding

This research received no specific grant from any funding agency in the public, private, or not-for-profit sectors.

Availability of data and materials

All patient data are available in the hospital medical records.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent for publication

The patient described in this article consented to the submission of this case report to the journal. Written informed consent for the publication of anonymized case details was obtained from the patient. A copy of the written consent form is available.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Department of Neurosurgery, Kitakyushu Municipal Yahata Hospital, 2-6-2 Ogura, Yahata-Higashi, Kitakyushu, Fukuoka 805-8534, Japan. ²Department of Neurosurgery, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu, Fukuoka 807-8555, Japan.

Received: 20 July 2021 Accepted: 9 February 2022

Published online: 03 March 2022

References

1. Baguley IJ, Perkes IE, Ortega J, Rabinstein A, Dolce G, Hendricks HT. Paroxysmal sympathetic hyperactivity after acquired brain injury: consensus on conceptual definition, nomenclature, and diagnostic criteria. *J Neurotrauma*. 2014;31:1515–20.
2. Zheng RZ, Lei ZQ, Yang RZ, Huang GH, Zhang GM. Identification and management of paroxysmal sympathetic hyperactivity after traumatic brain injury. *Front Neurol*. 2020;11:81.
3. Thomas A, Greenwald BD. Paroxysmal sympathetic hyperactivity and clinical considerations for patients with acquired brain injuries: a narrative review. *Am J Phys Med Rehabil*. 2019;98:65–72.
4. Choi HA, Jeon SB, Samuel S, Allison T, Lee K. Paroxysmal sympathetic hyperactivity after acute brain injury. *Curr Neurol Neurosci Rep*. 2013;13:370.
5. Lump D, Moyer M. Paroxysmal sympathetic hyperactivity after severe brain injury. *Current Neurol Neurosci Rep*. 2014;14:494.
6. Hendricks HT, Heere AH, Vos PE. Dysautonomia after severe traumatic brain injury. *Eur J Neurol*. 2010;17:1172–7.
7. Rabinstein AA. Paroxysmal sympathetic hyperactivity in the neurological intensive care unit. *Neurol Res*. 2007;29:680–2.
8. Perkes I, Baguley IJ, Nott MT, Menon DK. A review of paroxysmal sympathetic hyperactivity after acquired brain injury. *Ann Neurol*. 2010;68:126–35.
9. Rabinstein AA, Benarroch EE. Treatment of paroxysmal sympathetic hyperactivity. *Curr Treat Options Neurol*. 2008;10:151–7.
10. Baguley IJ, Heriseanu RE, Cameron ID, Nott MT, Slewa-Younan S. A critical review of the pathophysiology of dysautonomia following traumatic brain injury. *Neurocrit Care*. 2007;8:293–300.
11. Meyfroidt G, Baguley IJ, Menon DK. Paroxysmal sympathetic hyperactivity: the storm after acute brain injury. *Lancet Neurol*. 2017;16:721–9.
12. Gao B, Pollock JA, Hinson HE. Paroxysmal sympathetic hyperactivity in hemispheric intraparenchymal haemorrhage. *Ann Clin Transl Neurol*. 2014;1:215–9.
13. Kitagawa T, Ishikawa H, Yamamoto J, Ota S. Takotsubo cardiomyopathy and neurogenic pulmonary edema after carotid endarterectomy. *World Neurosurg*. 2019;124:157–60.
14. Shiozaki T, Taneda M, Kishikawa M, Iwai A, Sugimoto H, Yoshioka T, et al. Transient and repetitive rises in blood pressure synchronized with plasma catecholamine increases after head injury: Report of two cases. *J Neurosurg*. 1993;78:501–4.
15. Feng Y, Zheng X, Fang Z. Treatment progress of paroxysmal sympathetic hyperactivity after acquired brain injury. *Pediatr Neurosurg*. 2015;50:301–9.
16. Samuel S, Allison TA, Lee K, Choi HA. Pharmacologic management of paroxysmal sympathetic hyperactivity after brain injury. *J Neurosci Nurs*. 2016;48:82–9.
17. Fernandez-Ortega JF, Prieto-Palomino MA, Munoz-Lopez A, Lebron-Gallardo M, Cabrera-Ortiz H, Quesada-Garcia G. Prognostic influence and computed tomography findings in dysautonomic crises after traumatic brain injury. *J Trauma*. 2006;61:1129–33.
18. 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;27:1945–50.
19. Hinson HE, Puybasset L, Weiss N, Perlberg V, Benali H, Galanaud D, et al. Neuroanatomical basis of paroxysmal sympathetic hyperactivity: a diffusion tensor imaging analysis. *Brain Inj*. 2015;29:455–61.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Submit your manuscript to a SpringerOpen® journal and benefit from:

- Convenient online submission
- Rigorous peer review
- Open access: articles freely available online
- High visibility within the field
- Retaining the copyright to your article

Submit your next manuscript at ► [springeropen.com](https://www.springeropen.com)