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Diagnosis and Management of Patients with Paroxysmal Sympathetic Hyperactivity following Acute Brain Injuries Using a Consensus-Based Diagnostic Tool: A Single Institutional Case Series

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Paroxysmal sympathetic hyperactivity (PSH) is a distinct syndrome of episodic sympathetic hyperactivities following severe acquired brain injury, characterized by paroxysmal transient fever, tachycardia, hypertension, tachypnea, excessive diaphoresis and specific posturing. PSH remains to be an under-recognized condition with a diagnostic pitfall especially in the intensive care unit (ICU) settings due to the high prevalence of concomitant diseases that mimic PSH. A consensus set of diagnostic criteria named PSH-Assessment Measure (PSH-AM) has been developed recently, which is consisted of two components: a diagnosis likelihood tool derived from clinical characteristics of PSH, and a clinical feature scale assigned to the severity of each sympathetic hyperactivity. We herein present a case series of patients with PSH who were diagnosed and followed by using PSH-AM in our tertiary institutional medical and surgical ICU between April 2015 and March 2017 in order to evaluate the clinical efficacy of PSH-AM. Among 394 survivors of 521 patients admitted with acquired brain injury defined as acute brain injury at all levels of severity regardless of the presence of altered consciousness, including traumatic brain injury, stroke, infectious disease, and encephalopathy, 6 patients (1.5%) were diagnosed as PSH by using PSH-AM. PSH-AM served as a useful scoring system for early objective diagnosis, assessment of severity, and serial evaluation of treatment efficacy in the management of PSH in the ICU settings. In conclusion, critical care clinicians should consider the possibility of PSH and can use PSH-AM as a useful diagnostic and guiding tool in the management of PSH.

Keywords: acquired brain injury; critical care; dysautonomia; paroxysmal sympathetic hyperactivity; sympathetic storm
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Introduction

In 1954, Penfield and Jasper reported for the first time a syndrome of episodic sympathetic hyperactivity following antecedent acquired brain injury (Penfield and Jasper 1954). This syndrome is characterized by paroxysmal transient fever, tachycardia, hypertension, tachypnea, excessive diaphoresis and posturing that occur spontaneously or are triggered in response to a non-painful physical stimulus such as endotracheal tube suctioning and passive body position changing, and may arise secondary to a wide range of etiologies including traumatic brain injury, hypoxic-ischemic encephalopathy and stroke (Perkes et al. 2010; Fernandez-Ortega et al. 2012; Meyer 2014; Takahashi et al. 2015).

Although this condition has gained increasing attention in view of its clinical burden such as morbidity, weight loss, dehydration, infections, interfering with rehabilitation, and longer length of stay in intensive care unit (ICU), different sets of diagnostic criteria and > 30 nomenclatures (e.g., dysautonomia, sympathetic storm, autonomic dys-

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function syndrome, etc.) have been proposed, leading to diagnostic confusion in this disorder (Perkes et al. 2010; Baguley et al. 2014). Even conceptual definition has not been established and standardized clinical diagnostic criteria have never been developed. Furthermore, pharmacological management of the sympathetic hyperactivities is challenging with limited evidence available to guide decision making (Rabinstein and Benarroch 2008; Samuel et al. 2016).

In 2014, Baguley et al. proposed that the term "paroxysmal sympathetic hyperactivity" (PSH) be used to identify the condition as defined ''a syndrome, recognized in a subgroup of survivors of severe acquired brain injury, of simultaneous, paroxysmal transient increases in sympathetic (elevated heart rate, blood pressure, respiratory rate, temperature, sweating) and motor (posturing) activity" (Baguley et al. 2014). They also developed a diagnostic tool named "PSH-Assessment Measure (PSH-AM)" in order to establish standardized diagnostic criteria and to help to guide the clinical management of PSH (Baguley et al. 2014) (Table 1). PSH-AM is consisted of two components: 1) a diagnosis likelihood tool derived from 11 clinical characteristics of PSH, and 2) a clinical feature scale assigned to the severity of each sympathetic hyperactivity. However, the usefulness of this consensus-based new diagnostic tool remains to be elucidated in clinical settings.

We herein present a case series of patients with PSH who were diagnosed and followed by using PSH-AM in a single institutional medical and surgical ICU in order to evaluate the clinical efficacy of PSH-AM.

Case Presentations

Among 1,492 patients admitted to our tertiary institutional medical and surgical ICU between April 2015 and

Table 1. Paroxysmal sympathetic hyperactivity-assessment measure (Baguley et al. 2014).

Clinical Feature Scale (CFS)	0	1	2	3
Heart rate (/minute)	< 100	100-119	120-139	≥ 140
Respiratory rate (/minute)	< 18	18-23	24-29	≥ 30
Systolic blood pressure (mmHg)	< 140	140-159	160-179	≥ 180
Temperature (℃)	< 37	37-37.9	38-38.9	≥ 39
Sweating	Nil	Mild	Moderate	Severe
Posturing during episodes	Nil	Mild	Moderate	Severe
			CFS subtotal	
Diagnostic Likelihood Tool (DLT) (Score 1 point for each feature present)				
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				
Features persist despite treatment of alternative 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				
			DLT subtotal	
Combined total (CFS + DLT)				
PSH diagnostic likelihood			Unlikely	< 8
			Possible	8-16
			Probable	≥ 17

PSH, paroxysmal sympathetic hyperactivity.

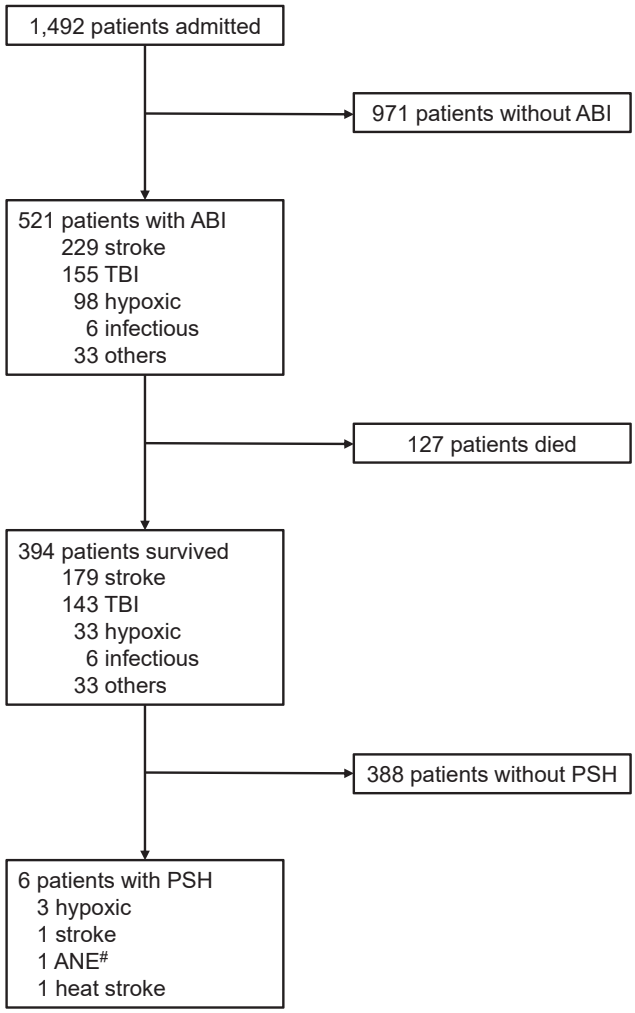

Fig. 1. Enrollment, etiologies of acquired brain injury, and outcome.
The flow diagram summarizes selection process of the study population. '33 others' include 25 patients with carbon monoxide poisoning, 5 with heat stroke, 2 with cerebral venous sinus thrombosis, and 1 with autoimmune encephalitis. #secondary to a virus-associated acute demyelinating encephalomyelitis. ABI, acquired brain injury; ANE, acute necrotizing encephalopathy; PSH, paroxysmal sympathetic hyperactivity; TBI, traumatic brain injury.

March 2017, a total of 521 patients suffered from acquired brain injury, which was defined as an acute injury to the brain acquired after birth at all levels of severity regardless of the presence of altered consciousness, including traumatic brain injury, stroke, infectious disease, and encephalopathy (Perkes et al. 2010, Hughes and Rabinstein 2014). Among the 394 survivors of them, 6 patients (1.5%) were diagnosed with PSH by using PSH-AM (Baguley et al. 2014) (Fig. 1 and Table 2). In all the patients, we used the criteria in PSH-AM to diagnose PSH after thorough exclusion of differential diagnoses in the clinical ICU settings, including seizures, sepsis, sedation withdrawal, and neuroleptic malignant syndrome (Rabinstein and Benarroch 2008), and subsequently monitored the total score of PSH-AM on a daily basis as an index of severity level and treatment efficacy for PSH. The brief presentations of each patient are described as follows.

Patient 1

A 56-year-old man with a history of type 2 diabetes mellitus, hypertension and chronic kidney disease presented with out-of-hospital ventricular fibrillation due to acute myocardial infarction. Following a successful resuscitation using extracorporeal cardiopulmonary resuscitation (ECPR) and primary percutaneous coronary intervention, he was admitted to our ICU for the treatment of post-cardiac arrest syndrome including targeted temperature management (TTM). The total time from cardiac arrest to return of spontaneous circulation (ROSC) was 66 minutes. He showed persistent disturbance of consciousness due to hypoxic-ischemic encephalopathy and multiple cerebral infarctions (Fig. 2). On day 5, he developed episodic paroxysmal increases in heart rate, blood pressure, respiratory rate, and body temperature, accompanied with severe sweating. These PSH-like features were detected 5 to 15 times a day thereafter. On day 14, PSH-AM reached as high as 20 (Fig. 3), and he was diagnosed as PSH. He was treated with a cardio-selective β1-blocker, bisoprolol, which had been initiated earlier as a drug of choice for acute myocardial infarction at a low starting dose and was up-titrated to the maximal maintenance dose. The frequency and

Table 2. Case series of paroxysmal sympathetic hyperactivity.

Age	Sex	ABI	GCS on admission	Onset of PSH features	Diagnosis	Treatment	GCS on discharge	CPC on discharge
56	M	HIE	E1V1M1	day 5	day 14	β	E4VTM5	3
73	M	CI	E4V1M6	day 2	day 43	β, GABA	E4VTM6	3
14	F	HIE	E1V1M1	day 3	day 12	β, GABA	E4V2M5	3
49	F	HIE	E1V1M1	day 4	day 17	GABA	E4VTM6	3
44	M	ANE	E4V1M5	day 8	day 9	None	E4VTM6	3
85	M	Heat stroke	E4V1M4	day 2	day 30	β	E4V2M5	3

ABI, acquired brain injury; ANE, acute necrotizing encephalopathy; β, β-blocker; CI, cerebral infarction; CPC, cerebral performance category; F, female; GABA, gabapentin; GCS, Glasgow Coma Scale; HIE, hypoxic-ischemic encephalopathy; M, male; PSH, paroxysmal sympathetic hyperactivity.

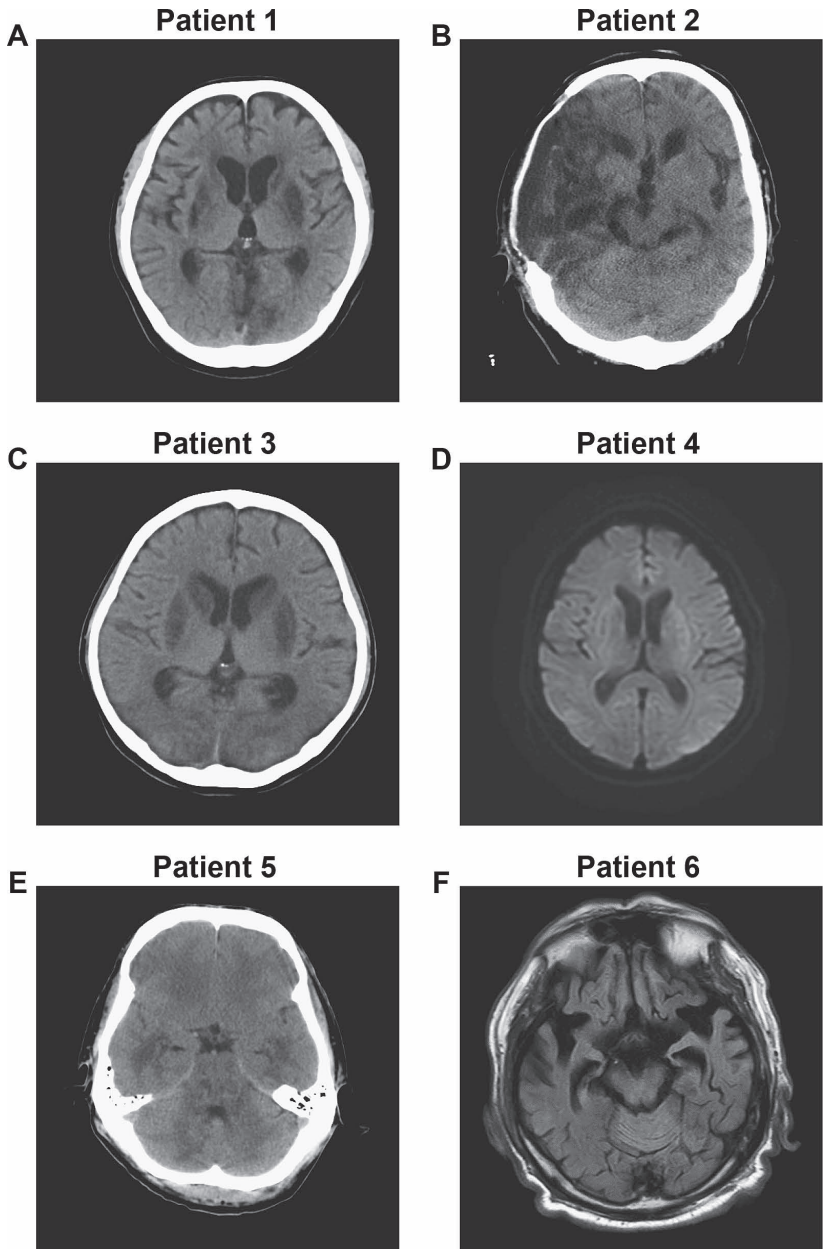

Fig. 2. The images of head computed tomography and magnetic resonance imaging.
(A) Computed tomography of the patient 1 on day 18 showed multiple cerebral infarctions in the left cerebellar hemisphere, right basal ganglions, and bilateral occipital lobes. (B) Computed tomography of the patient 2 on day 34 showed a large cerebral infarction in the right middle cerebral artery territory. (C) Computed tomography of the patient 3 on day 36 showed low density areas situated bilaterally in the corpus striatum, occipital lobes and watershed areas, consistent with hypoxic-ischemic changes. (D) Diffusion-weighted magnetic resonance imaging of the patient 4 on day 30 showed high intensity areas located in the bilateral putamen periphery, corpus striatum, and parietal, temporal and occipital lobes, consistent with hypoxic-ischemic changes. (E) Computed tomography of the patient 5 on day 8 showed diffuse low density areas in the bilateral cerebral and cerebellar white matters, pons, and hippocampi, associated with sulcal narrowing due to brain edema. (F) Fluid-attenuated inversion recovery magnetic resonance imaging of the patient 6 on day 7 showed diffuse high intensity areas in the cerebellum, suggestive of changes due to heat stroke.

severity of paroxysmal hypertension, tachycardia, tachypnea and hyperthermia diminished gradually in accordance with the up-titration of bisoprolol, where PSH-AM served as an objective monitor of the treatment efficacy (Fig. 3). However, he required occasional fluid replacement therapy because of dehydration secondary to paroxysmal excessive diaphoresis. On day 63, he was discharged from our hospital with Glasgow Coma Scale (GCS) score of E4VTM5 and Cerebral Performance Category (CPC) of 3.

Patient 2

A 73-year-old man who had a history of hypertrophic

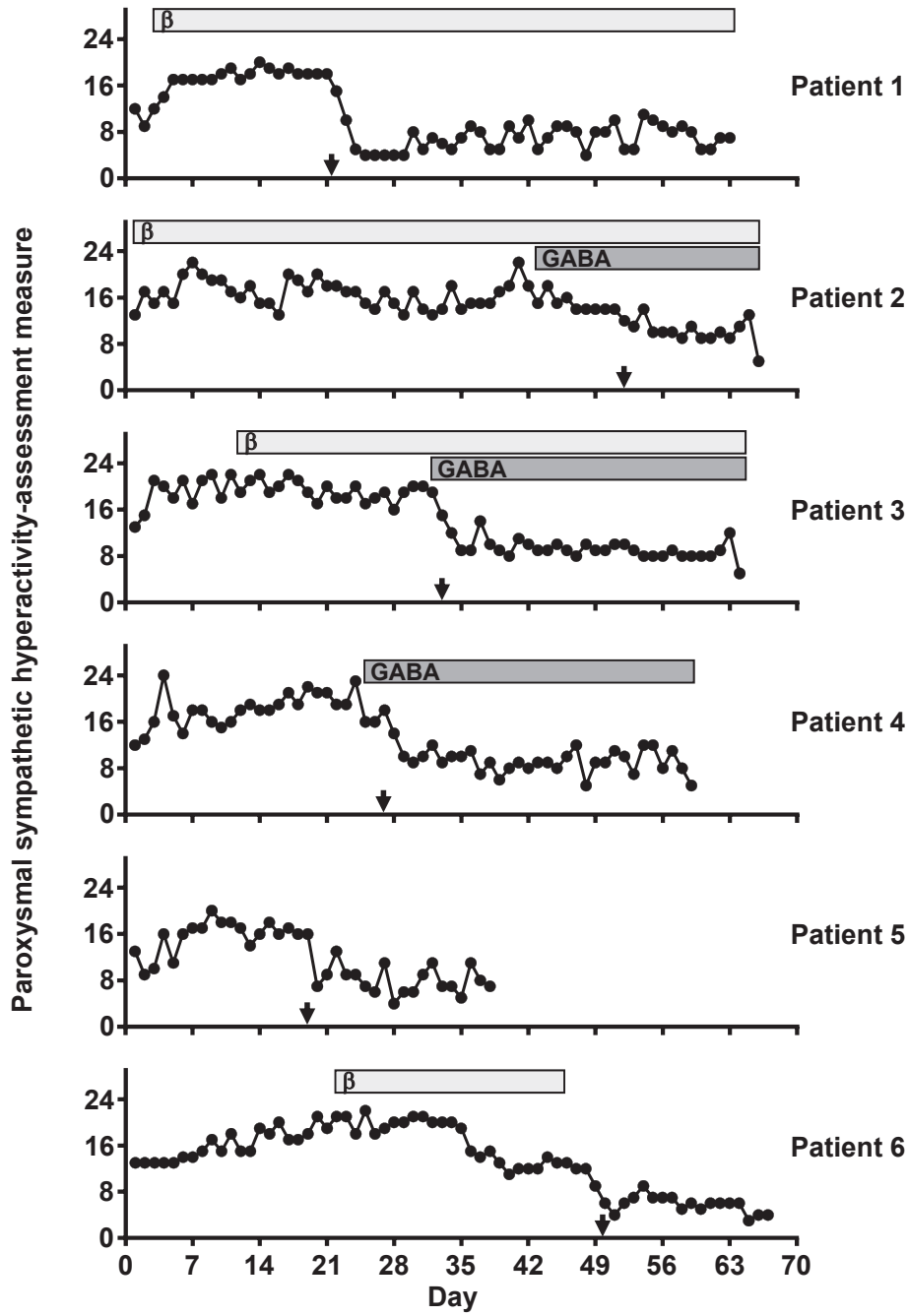

Fig. 3. The clinical courses of the paroxysmal sympathetic hyperactivity-assessment measure.
Paroxysmal sympathetic hyperactivity (PSH) diagnostic likelihood is considered to be 'Unlikely' with PSH-Assessment Measure (PSH-AM) < 8, 'Possible' with PSH-AM 8-16, and 'Probable' with PSH-AM ≥ 17. Each arrow indicates a discharge from intensive care unit to general ward. *β*, *β*-blocker; GABA, gabapentin.

cardiomyopathy and atrial fibrillation was admitted to our ICU for the treatment of a large cerebral infarction caused by cardiogenic embolism in the right middle cerebral artery. On the first day, he underwent an emergency decompressive craniectomy in order to reduce the elevated intracranial pressure secondary to cerebral edema but developed persistent disturbance of consciousness (Fig. 2). From the second day, he exhibited paroxysmal increases in heart rate, blood pressure, respiratory rate, body temperature, and tone in the right upper limb twice to 7 times a day. *β*-Blockers and antipyretic agents were ineffective for these paroxysms. From day 18, episodic excessive diaphoresis emerged in conjunction with them, leading to significant weight loss and dehydration. We initially considered that his features were attributable to dehydration, central fever following his large cerebral infarction, and systemic inflammatory response syndrome secondary to concomitant pneumoniae and urinary tract infection. This resulted in a delayed diag-

nosis of PSH. After exclusion of alternative pathologic conditions, we diagnosed as PSH on the basis of PSH-AM on day 43, and administered gabapentin at an initial dose of 200 mg 3 times a day and up-titrated to 400 mg 3 times a day. The therapeutic effect of gabapentin was drastic; the PSH-related symptoms quickly diminished in frequency and severity from the day following the initiation of the treatment with gabapentin as represented by the consistent reduction in PSH-AM (Fig. 3). From day 63, we were able to taper the dosage of gabapentin to 200 mg 3 times a day without exacerbation of the PSH features. His GCS score and CPC on discharge on day 66 was E4VTM6 and 3, respectively.

Patient 3

A 14-year-old girl without past medical history presented with out-of-hospital cardiopulmonary arrest secondary to extensive necrosis of the small intestine caused by intestinal strangulation. The total time from cardiac arrest to ROSC, which was achieved by emergency medical technicians using 1 mg of adrenaline, was 10 minutes. She developed consciousness disturbance due to hypoxic-ischemic encephalopathy (Fig. 2) despite the intensive post-cardiac arrest care. From day 3, she showed all typical features of PSH that were refractory to β-blockers, anticonvulsant drugs, and benzodiazepines. The frequency of these episodes ranged from 3 to 20 a day with PSH-AM of 17 to 22, leading to a diagnosis of PSH in the second week of admission (Fig. 3). On day 32, we treated her condition with gabapentin at a dose of 400 mg 3 times a day, which provided swift remission of her symptoms with a marked reduction in PSH-AM. On day 64, she was discharged from our hospital with GCS score of E4V2M5 and CPC of 3.

Patient 4

A 49-year-old woman who had no past medical history presented with out-of-hospital cardiopulmonary arrest due to massive pulmonary embolism, which was resuscitated with ECPR and aggressive anticoagulation therapy. The total time from cardiac arrest to ROSC was 51 minutes. Although she received intensive post-cardiac arrest care including TTM, she developed persistent disturbance of consciousness due to hypoxic-ischemic encephalopathy (Fig. 2). On day 4, she showed episodic simultaneous increases in heart rate, respiratory rate and body temperature associated with beads of sweating and strong hypertonicity of the extremities during episodes. These PSH-like features were detected twice to 8 times each following day with PSH-AM of >17 (Fig. 3) and were resistant to benzodiazepines, opioids and non-steroidal anti-inflammatory drugs. On day 17, she was diagnosed with PSH after exclusion of differential diagnoses, including sepsis and seizures. On day 25, she was treated with gabapentin, the dosage of which was 200 mg 3 times in the initial day and was up-titrated to 600 mg 3 times daily. Gabapentin demonstrated a dramatic effect on the PSH features within a few days of starting the treatment as evidenced by the immediate reduction in PSH-AM (Fig. 3). Paroxysmal excessive diaphoresis recurred soon after the dosage of gabapentin was tapered from 600 mg 3 times daily to 400 mg 3 times daily, and vice versa, indicating the obvious effects of gabapentin on the PSH features. On day 59, she was discharged from our hospital with GCS score of E4VTM6 and CPC of 3.

Patient 5

A 44-year-old man without past medical history was admitted to our ICU due to a virus-associated acute demyelinating encephalomyelitis. He developed secondary acute necrotizing encephalopathy with resultant disturbed consciousness (Fig. 2). From day 8, PSH-like features manifested as transient simultaneous increases in heart rate, blood pressure, respiratory rate and body temperature, severe sweating and hypertonic posturing of his extremities with or without preceding endotracheal tube suctioning or position changes. Although PSH-AM score increased up to 20 on day 9, his paroxysms showed a gradual decline without specific medical interventions (Fig. 3). His GCS score and CPC on discharge on day 38 was E4VTM6 and 3, respectively.

Patient 6

An 85-year-old man who had hypertension and mild cognitive impairment presented with heat stroke complicated with multiple organ failure. He developed disturbance of consciousness due to the primary brain damage caused by the profound hyperthermia (Fig. 2). From the second day of admission, he showed paroxysmal simultaneous increases in heart rate, blood pressure, respiratory rate and body temperature several times daily. From the second week of admission, these PSH-like features were associated with mild sweating and moderate increases in tone in the extremities with PSH-AM around 20 (Fig. 3). Although concomitant septic pneumonia delayed the definitive diagnosis, he was diagnosed with PSH and was treated with bisoprolol on day 30. His PSH features gradually improved over a couple of weeks (Fig. 3). On day 45, bisoprolol was discontinued because of hypotension without relapse of the PSH episodes. On day 67, he was discharged from our hospital with GCS score of E4V2M5 and CPC of 3.

Discussion

The present case series highlighted two major clinical implications. First, critical care clinicians need to consider the diagnosis of PSH to be a high possibility when patients with severe acquired brain injury are accompanied with PSH-like features, such as episodic and recurrent fever, tachycardia, hypertension, tachypnea, excessive diaphoresis and specific posturing. Second, PSH-AM may be a useful scoring system for early objective diagnosis, assessment of severity, and serial evaluation of treatment efficacy in the management of PSH. To the best of our knowledge, this is

the first case series to demonstrate the potential usefulness of PSH-AM in the management of patients with PSH after acquired brain injury.

First, a high index of suspicious is important in order to facilitate early recognition and diagnosis of PSH, a common complication following severe brain injuries that is otherwise prone to be an overlooked condition. PSH can be clinical burden with therapeutic potential such as morbidity, weight loss, dehydration, infections, unnecessary tests and interventions, interfering with rehabilitation, and longer length of stay in ICU (Perkes et al. 2010; Fernandez-Ortega et al. 2012; Baguley et al. 2014; Meyer 2014; Takahashi et al. 2015). Although the prevalence of PSH is not uncommon in patients with acute brain damage, PSH remains an under-recognized condition with a diagnostic pitfall in the ICU settings in particular (Hughes and Rabinstein 2014). This is, at least in part, because PSH is diagnosed by exclusion of other pathologic state including seizures, sepsis, sedation withdrawal, central fever, pulmonary embolism, and neuroleptic malignant syndrome, all of which are common comorbidities in critically ill patients and thus make the correct diagnosis of PSH challenging (Rabinstein and Benarroch 2008, Wang and Manley 2008, Hughes and Rabinstein 2014). In all 6 patients of this series, we measured thyroid hormones to rule out hyperthyroidism and performed computed tomography to exclude hyperadrenalism due to adrenal tumors including pheochromocytoma. Indeed, PSH can be under-diagnosed in the developed countries as in the clinical practice in Japan, where nomenclature in our own language referring to this condition has yet to be proposed and only a few case reports are available (Okada et al. 2014; Fujimoto et al. 2016; Kumagai et al. 2016). As mentioned in the initial report (Baguley et al. 2014), non-specific nature of PSH-AM in the differential diagnoses may be a limitation of this diagnostic tool in the ICU settings; the present patients 2 and 6 required a few weeks to be diagnosed as PSH after onset of the PSH features due to the concomitant diseases that mimicked PSH. Although early diagnostic biomarkers of PSH have yet to be developed, a very recent study has shown that plasma catecholamine concentrations markedly increased during PSH episodes (Fernandez-Ortega et al. 2017), indicating additional usefulness of catecholamine levels for early diagnosis of this disorder. More recently, an observational cohort study of traumatic brain injury patients with impaired consciousness (GCS score $\leq$ 12) has shown that early fever might be an indication of autonomic dysfunction; among the clinical feature scale items of PSH-AM (Table 1), higher temperature scores within 3 days after ICU admission were associated with the development of PSH, indicating that early fever may be a herald of PSH following severe traumatic brain injury (Hinson et al. 2017). In contrast, our PSH patients exhibited higher scores of blood pressure, respiratory rate, and heart rate than those of temperature before being diagnosed with PSH. The dissimilarities between the two cohorts may be attributable to the differences in etiology of brain injury, therapeutic interventions including TTM, and concomitant diseases, which might affect body temperature. PSH can be early diagnosed with high awareness of its possibility after exclusion of differential diagnoses; sepsis, seizures, alternative brain injuries, and arrhythmias, where PSH-AM may serve as reliable diagnostic criteria.

Second, as suggested partly in the original report (Baguley et al. 2014), PSH-AM may provide a useful index of severity level and treatment efficacy in the management of patients with PSH. In the present case series, PSH developed secondary to a variety of acute brain injuries, irrespective of age and sex, however, we were able to exclude other presumed causes of PSH-like features and diagnose PSH using PSH-AM. Moreover, PSM-AM served as a useful index of the treatment effect as evidenced in the present case series (Fig. 3). Pharmacological management of the paroxysms of PSH is challenging with paucity of evidence available to guide treatment strategies. A number of medications have been used for the control of symptoms of PSH, including morphine, β-blockers, benzodiazepines, baclofen, clonidine, and gabapentin (Rabinstein and Benarroch 2008; Samuel et al. 2016). In the present case series, benzodiazepines, opioids, and non-steroidal anti-inflammatory drugs had only a minimal effect on the features of PSH while β-blockers were administered in most of our patients with variable effects on the episodes of PSH. In contrast, gabapentin exerted a prompt effect on the symptoms of PSH, consistent findings with a previous report demonstrating immediate efficacy of gabapentin in patients with PSH following severe traumatic brain injury (Baguley et al. 2007). As shown clearly in Fig. 3, serial recordings of the daily score of PSH-AM allowed us to monitor the clinical trends and to assess the treatment effects, and provided us with useful information for making a decision in the pharmacological management of PSH, indicating a promising potential of PSH-AM as a useful guide for diagnosis and management of PSH. A limitation of the present study was that there were no control groups. Further observation and prospective trials are warranted to elucidate whether the management of PSH guided by PSH-AM can improve outcome of the patients with this condition.

PSH remains an under-recognized condition and a diagnostic pitfall with major clinical issues. The course of our patients provided two important clinical implications; PSH is a considerable complication in patients with acute brain injury that can be diagnosed with a high index of suspicious, and PSH-AM may provide a useful guidance on the diagnosis and management of PSH. In conclusion, critical care clinicians should consider the possibility of PSH in patients with severe acquired brain injury showing a simultaneous fever, tachycardia, hypertension, tachypnea, excessive diaphoresis, and posturing in an episodic and recurrent manner, and can use PSH-AM as a diagnostic and guiding tool in the clinical management of this otherwise underdiagnosed disorder.

Author Contributions

S.G. conceived and designed the study, analyzed the data, and wrote the paper. S.I., A.N., Y.K., M.F., D.K., and R.N. joined the discussion. H.S. and S.K. organized the study and made critical revisions to the manuscript. All authors read, revised, and approved the final report.

Conflict of Interest

The authors declare no conflict of interest.

References

Baguley, I.J., Heriseanu, R.E., Gurka, J.A., Nordenbo, A. & Cameron, I.D. (2007) Gabapentin in the management of dysautonomia following severe traumatic brain injury: a case series. *J. Neurol. Neurosurg. Psychiatry*, **78**, 539-541.

Baguley, I.J., Perkes, I.E., Fernandez-Ortega, J.F., Rabinstein, A.A., Dolce, G. & Hendricks, H.T. (2014) Paroxysmal sympathetic hyperactivity after acquired brain injury: consensus on conceptual definition, nomenclature, and diagnostic criteria. *J. Neurotrauma*, **31**, 1515-1520.

Fernandez-Ortega, J.F., Baguley, I.J., Gates, T.A., Garcia-Caballero, M., Quesada-Garcia, J.G. & Prieto-Palomino, M.A. (2017) Catecholamines and paroxysmal sympathetic hyperactivity after traumatic brain injury. *J. Neurotrauma*, **34**, 109-114.

Fernandez-Ortega, J.F., Prieto-Palomino, M.A., Garcia-Caballero, M., Galeas-Lopez, J.L., Quesada-Garcia, G. & Baguley, I.J. (2012) Paroxysmal sympathetic hyperactivity after traumatic brain injury: clinical and prognostic implications. *J. Neurotrauma*, **29**, 1364-1370.

Fujimoto, T., Fukuta,Y. & Kato, M. (2016) Case report: suspected paroxysmal sympathetic hyperactivity following hypoxia. *Tokushima Red Cross Hospital Medical Journal*, **21**, 81-84 (in Japanese, abstract in English).

Hinson, H.E., Schreiber, M.A., Laurie, A.L., Baguley, I.J., Bourdette, D. & Ling, G.S. (2017) Early fever as a predictor of paroxysmal sympathetic hyperactivity in traumatic brain injury. *J. Head Trauma Rehabil*., doi: 10.1097/htr.0000000000000271. [Epub ahead of print].

Hughes, J.D. & Rabinstein, A.A. (2014) Early diagnosis of paroxysmal sympathetic hyperactivity in the ICU. *Neurocrit. Care*, **20**, 454-459.

Kumagai, K, Hirose, Y., Yoshida, S. & Inoue, Y. (2016) A case of paroxysmal sympathetic hyperactivity with fluctuation of symptoms. *Journal of Japanese Association for Acute Medicine*, **27**, 776-781. (in Japanese, abstract in English).

Meyer, K.S. (2014) Understanding paroxysmal sympathetic hyperactivity after traumatic brain injury. *Surg. Neurol. Int*., **5**, S490-492.

Okada, Y., Inagawa, H., Kojima, N., Yamaguchi, K. & Sasaki, N. (2014) Two cases of paroxysmal sympathetic hyperactivity following head injury. *J. Jpn. Soc. Intensive Care Med*., **21**, 268-272 (in Japanese, abstract in English).

Penfield, W. & Jasper, H. (1954) Autonomic seizures. In: *Epilepsy and the Functional Anatomy of the Human Brain,* edited by Penfield, W. & Jasper, H. J & A Churchill Ltd., London, pp. 412-437.

Perkes, I., Baguley, I.J., Nott, M.T. & Menon, D.K. (2010) A review of paroxysmal sympathetic hyperactivity after acquired brain injury. *Ann. Neurol*., **68**, 126-135.

Rabinstein, A.A. & Benarroch, E.E. (2008) Treatment of paroxysmal sympathetic hyperactivity. *Curr. Treat. Options Neurol*., **10**, 151-157.

Samuel, S., Allison, T.A., Lee, K. & Choi, H.A. (2016) Pharmacologic management of paroxysmal sympathetic hyperactivity after brain injury. *J. Neurosci. Nurs*., **48**, 82-89.

Takahashi, C., Hinson, H.E. & Baguley, I.J. (2015) Autonomic dysfunction syndromes after acute brain injury. *Handb. Clin. Neurol*., **128**, 539-551.

Wang, V.Y. & Manley, G. (2008) Recognition of paroxysmal autonomic instability with dystonia (PAID) in a patient with traumatic brain injury. *J. Trauma*, **64**, 500-502.