

# Utility of Serum Procalcitonin in Diagnosing Paroxysmal Sympathetic Hyperactivity in Patients with Traumatic Brain Injury

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## ABSTRACT

**Background:** Paroxysmal sympathetic hyperactivity (PSH) is a grave entity affecting patients following traumatic brain injury (TBI). It presents with cyclic and simultaneous fever, posturing, and other symptoms of sympathetic hyperactivity. Lack of diagnostic tests or biochemical markers and its propensity to mimic other common causes of fever in the neurotrauma intensive care unit (ICU) result in clinical dilemmas and management delay.

**Case descriptions:** We present a case series of four patients (two adults and two pediatrics) with TBI who developed PSH during ICU stay. These patients presented with fever along with variable symptoms of sympathetic hyperactivity. However, the value of serum procalcitonin (PCT) was not elevated, and management of PSH was started. Serial monitoring of PCT helped in differentiating fever due to PSH from sepsis and thus the institution of appropriate and timely treatment of PSH and also helped to use antibiotics rationally.

**Conclusion:** The use of serum PCT in differentiating sepsis from systemic inflammatory reaction and its role in the initiation and titration of antibiotics are well described. PSH is a common entity after TBI, causing episodic fever and sympathetic hyperactivity, often confused with infectious pathology. Our report proposes the role of serum PCT in differentiating PSH from infectious etiology and management of two different clinical entities.

**Keywords:** Paroxysmal sympathetic hyperactivity, PCT, Sepsis, Traumatic brain injury (TBI).

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## INTRODUCTION

Paroxysmal sympathetic hyperactivity (PSH) is a syndrome of simultaneous, paroxysmal transient sympathetic [increased heart rate, blood pressure (BP), respiratory rate, temperature, sweating, and motor (posturing)] activity generally in response to non-noxious stimuli in a subgroup of survivors of severe acquired brain injury.<sup>1</sup> The time of onset of symptoms is variable, ranging from the first few hours of injury to months. It adds to morbidity and mortality in neurocritical patients. PSH often leads to unnecessary workup, medication use, prolonged hospital stays, and poor outcome.

A recently proposed clinical scoring system known as PSH assessment measure consisting of clinical feature scale score and diagnosis likelihood tool describes the clinical criteria to diagnose PSH.<sup>1</sup> This categorizes PSH as unlikely, possible, and probable. However, the lack of any clear diagnostic test or biochemical markers hampers its definite diagnosis, and PSH remains a diagnosis of exclusion. Early fever in ICU following traumatic brain injury (TBI) is a predictor of PSH. Nevertheless, the incidence of fever is high in the neurotrauma intensive care unit (ICU).<sup>2</sup> Paroxysms of high-grade fever with diaphoresis and with or without motor posturing has shown significant association with PSH, but at the same time patients with a history of penetrating or blunt trauma in ICU, on the ventilator, and with multiple invasive devices are quite likely to have a fever of infectious origin that may also be accompanied by similar autonomic symptoms of varying intensity. Sedation in ICU might mask the sympathetic overactivity associated with PSH. The administration of empirical antibiotics in trauma patients decreases the likelihood of isolating an organism from

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culture. Distinguishing PSH from infection often becomes a clinical challenge.

Procalcitonin (PCT) has been found to differentiate sepsis from systemic inflammatory response syndrome with a pooled sensitivity and specificity of 0.77 and 0.79, respectively. Initiation and continuation of antibiotics based on initial PCT levels have been proposed.<sup>3</sup> We utilized PCT for differentiating infective fever and fever due to PSH since both entities have an overlapping presentation but different management approaches. We present a series of four patients with TBI wherein serial PCT testing helped

in early diagnosis of PSH and institution of appropriate treatment. Consent was obtained from the patient's family for publication.

### CASE DESCRIPTIONS

We describe a series of four patients, two adults and two pediatric, admitted to neurotrauma ICU after TBI and developed a fever during the first week (ranging from 2nd to 7th day) (Table 1). All patients were intubated and were mechanically ventilated and sedated with intravenous fentanyl and midazolam. The fever episodes were accompanied by variable symptoms of sympathetic hyperactivity like tachycardia, tachypnea, rise in systolic BP, posturing, and diaphoresis as described in Table 1. Case 2 had episodes of desaturation up to 85% on pulse oximeter during posturing episodes.

The demographic and clinical features of the patients are summarized in Table 1. Since all patients suffered TBI and nosocomial infections, a common cause of fever at 48 hours could not be ruled out. However, episodic features of fever and sympathetic activity

also pointed toward PSH. The urge of escalating antibiotics is usually immense during such situations. Serum PCT levels were sent at the time of appearance of fever in all the patients. The levels were not elevated, which ruled out the infectious cause and favored toward the diagnosis of PSH. So the patients were managed by prescribing treatment for PSH.

Patients with predominant tachycardia and spasticity were started on propranolol and baclofen. Case 2 required additional sedation with dexmedetomidine. However, Case 3 had predominant tachycardia and was managed only with propranolol.

This was followed by serial monitoring of PCT levels. During the second week, both adult patients (Cases 1 and 2) had elevated levels of serum PCT (28.7 and 71.8 ng/mL, respectively) and were investigated further for the presence of infections. There was microbial growth in the blood culture of both the patients, and culture-specific antimicrobials were added along with drugs used for the management of PSH. Both the pediatric patients (Cases 3 and 4) showed no rise in serum PCT, and hence, no antibiotic escalation was done.

**Table 1:** Clinical course of the patients

	Case 1	Case 2	Case 3	Case 4
Age in years and sex	25 and male	2 and male	32 and male	8 and male
Mechanism of injury	Road traffic accident	Fall from height	Road traffic accident	Road traffic accident
Admission GCS	E1V1M5	E1V1M5	E2V3M5	E2V2M4
Intubation and mechanical ventilation	Yes	Yes	Yes	Yes
Neurosurgical intervention	Conservative management	Conservative management	Conservative management	Conservative management
NCCT* head	Multiple dot contusions Left frontal bone fracture with IVH**	Left temporal contusion Lt and Rt parietal bone fracture Bilateral IVH	Rt FTP fracture Subdural hemorrhage Midline shift and mass effect	Rt fronto-temporo-parietal hemorrhagic contusions IVH
First episode of fever and symptoms:	Day 2 (101°F) Yes	Day 7 (103.6°F) Yes	Day 4 (102°F) Yes	Day 5 (102°F) Yes
Tachycardia	Yes	Yes	Yes	Yes
Tachypnea	Yes	Yes	Yes	Yes
SBP elevation	Yes	Yes	Yes	Yes
Posturing	Yes	Yes	Yes	Yes
Diaphoresis				
Culture and PCT values (ng/mL) in the first week (on the appearance of symptoms)	No growth 0.18	No growth 0.30	No growth 0.28	No growth 0.11
Clinical feature scale	11	13	16	9
Diagnosis likelihood tool	10	10	10	9
Total score/PSH	21. Probable	23. Probable	26. Probable	18. Probable
Management drugs	Propranolol 20 mg BD Baclofen 10 mg BD	Propranolol 5 mg BD Baclofen 5 mg BD Dexmedetomidine 0.7 µg/kg/hr for 24 hrs	Propranolol 20 mg BD	Propranolol 5 mg BD Baclofen 5 mg BD
Subsequent clinical course	<b>Day 9:</b> PCT 28.7 ng/mL	<b>Day 15:</b> PCT 71.8 ng/mL	<b>Week 2</b>	<b>Week 2</b>
Culture and PCT values (ng/mL)	<b>Day 12:</b> Klebsiella growth in blood culture	<b>Day 17:</b> Klebsiella growth in blood culture	PCT 0.82 ng/mL No cultures found positive	PCT 0.56 ng/mL No cultures found positive
Revised management	Culture-sensitive antibiotics added	Culture-sensitive antibiotics added	–	–
Outcome	Symptoms gradually improved.	Death due to septic shock.	Symptoms gradually improved.	Symptoms gradually improved.

Along with clinical features, measuring PCT levels helped us in early differential diagnosis and appropriate management without unnecessary antibiotic escalation.

## DISCUSSION

PSH has a reported incidence of 7.7–33% and is predominantly observed after TBI (80%).<sup>1,2</sup> Other causes include hypoxic brain injury (9.7%), stroke (5.4%), post-cardiac arrest, and subarachnoid hemorrhage (SAH). PSH episodes are characterized by hyperthermia, hypertension, tachycardia, tachypnea, posturing, and diaphoresis. There are different stages of PSH manifestations; the first stage has a variable combination of symptoms that can remain masked due to sedation; the second stage is characterized by clusters of symptoms with the withdrawal of sedation, and the third stage witnesses a decline in dystonia and posturing, but residual muscle spasticity adds to morbidity and delayed rehabilitation.<sup>4</sup>

PSH symptoms in the first stage may not be overt in ICU in an acutely injured patient receiving sedatives and paralytics. However, early fever as a predictor of PSH in TBI should always be remembered.<sup>2</sup> Fever in ICU during the first week can be easily attributed to injury and infection due to multiple invasive lines and mechanical ventilation. Identifying the cause of fever is important for appropriate management.

Due to the similarity in symptoms and lack of any definite diagnostic test, diagnosis of PSH requires a high index of suspicion. This often leads to delay in diagnosis, misdiagnosis, inappropriate therapy, unwarranted side effects, and increased morbidity. Fever in neurologically injured can be attributed to include PSH, central fever, seizure, and sepsis along with other causes like neuroleptic malignant syndrome, malignant hyperthermia, and pulmonary embolism. In contrast to PSH which is mostly seen in TBI, central fever is seen in patients with SAH, intracranial hematoma, or ischemia. It is a continuous fever with no triggering factors and occurs within 24 to 72 hours of the injury, presence of relative bradycardia, and absence of motor posturing.<sup>3</sup> In our patients with lack of overt seizures, electrocardiographic abnormalities, no exposure to dopamine blockers, or inhalational anesthetics, normal thyroid profile ruled out other causes of fever.

Measurement of PCT along with clinical symptom levels helped us in timely differentiation between the two. All of our four patients had PSH symptoms within the first week of admission, and all had a fever as one of the manifestations (Table 1). PCT sent during the early phase of onset of fever was less than 1 ng/mL, and such low levels of PCT in the first few days after major trauma indicate noninfectious systemic response. Later, negative cultures reinforced the same. In our case, PCT assay helped in excluding infection as a cause of fever, leading to avoidance of unnecessary antibiotic administration during the first week. Subsequent PCT values showed an increasing trend in two out of the four patients indicating infective etiology, and appropriate antibiotics were instituted following the sensitivity report. We lost one patient to septic shock in whom PCT values jumped during the subsequent measurements.

Management of PSH includes identifying the triggers like change in position, urinary retention, or suctioning and avoiding them if possible and pharmacologic measures to abolish the symptoms.<sup>5</sup> Drugs target the opioid, GABA,  $\alpha$ -2, D2 receptors in the brain and spinal cord, and  $\alpha$  and  $\beta$  adrenoceptors in the periphery and brain. Drugs frequently used in the management include opioids,  $\alpha$  and  $\beta$  blockers, central  $\alpha$ -2 receptor agonists, benzodiazepine, gabapentin, and baclofen.<sup>7</sup> Other supportive measures include

prevention of fever, physiotherapy, and positioning to prevent contractures and nutritional supplementation.<sup>6</sup>

PCT is a calcitonin precursor and is a marker of bacterial infection. Healthy individuals have levels <0.05 ng/mL. It is a stable marker of bacterial infection with multiple advantages over C-reactive protein.<sup>7</sup> Blood cultures are the gold standard for the confirmation of bacteremia. However, blood cultures take time, and studies have shown that the decision to start or withhold antibiotics may be taken with PCT values alone or in combination with other markers like white blood cell count which are available rapidly.<sup>8</sup> Apart from this, its utility has also been described in differentiating systemic inflammatory response from infection in patients with SAH.<sup>9</sup> Beyond this, the role of PSH in the neurocritical care arena needs to be explored.

This report proposes the utilization of PCT for supporting the diagnosis of PSH. These are preliminary findings that need to be replicated in large studies. We also believe that PSH may coexist along with sepsis, and results and clinical symptoms need to be carefully observed.

## CONCLUSION

The use of serum PCT in differentiating sepsis from systemic inflammatory reaction and its role in the initiation and titration of antibiotics are well described. We wish to highlight the possible role of serum PCT as an ancillary marker to differentiate PSH from infectious etiology early in the course of the disease. The negative predictive value of a low or normal PCT level in PSH will help to rule out infection and stop antibiotic therapy and start appropriate timely management of PSH.

**Research Quality and Ethics Statement:** The authors of this manuscript declare that this scientific work complies with reporting quality, formatting, and reproducibility guidelines set forth by the EQUATOR Network. The authors also attest that this clinical investigation was not determined to require Institutional Review Board / Ethics Committee review. Finally, the authors have not registered this case report with Clinical Trial Registry.

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