# Paroxysmal Sympathetic Hyperactivity in Neurocritical Children: A Pilot Study

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## Abstract

**Background:** Paroxysmal sympathetic hyperactivity (PSH) is characterized by the abnormal excessive sympathetic response to acute cerebral insult. There is a paucity of data about this condition in children. This study was planned to analyze the incidence of PSH among children requiring neurocritical care and its association with the outcome.

**Materials and methods:** The study was conducted in the pediatric intensive care unit (PICU) of a tertiary care hospital over a period of 10 months. Children of age 1 month to 12 years admitted with neurocritical illnesses were included. Children who were declared brain dead after initial resuscitation were excluded from the study. The criterion laid by Moeller et al. was used for the diagnosis for PSH.

**Results:** During the study period, 54 children requiring neurocritical care were included in the study. The incidence of PSH was 5/54 (9.2%). Additionally, 30 (55.5%) children had less than four criteria for PSH and were termed as "incomplete PSH." Children with all four criteria for PSH had a significantly longer duration of mechanical ventilation, PICU stay, and higher PRISM III scores. Children with less than four criteria for PSH also had a longer duration of mechanical ventilation and stay. However, there was no significant difference in mortality.

**Conclusion:** Paroxysmal sympathetic hyperactivity is common in children with neurological illnesses admitted to the PICU and is associated with longer mechanical ventilation and stay in PICU. They also had higher illness severity scores. Timely diagnosis of the condition and appropriate management is required to improve the outcome of these children.

**Keywords:** Autonomic dysfunction, Incomplete paroxysmal sympathetic hyperactivity, Neurocritical illness, Paroxysmal sympathetic hyperactivity, Traumatic brain injury.

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## Highlights

- Paucity of data on the incidence of PSH in children with neurocritical illness.
- Children with features of PSH have a longer duration of PICU stay, ventilation, and higher pediatric risk of mortality score (PRISM) III scores compared to children without PSH.
- Even children with features of incomplete PSH had a longer duration of ventilation and PICU stay.

## Introduction

Acute cerebral insult from various causes such as trauma, anoxia, or encephalitis, sometimes ensues excessive sympathetic activity which is characterized by paroxysmal autonomic and motor hyperactivity. Paroxysmal sympathetic hyperactivity is characterized by episodic alteration in heart rate, blood pressure, respiratory rate, and temperature associated with dystonic posturing, diaphoresis, and pupillary abnormalities.[1]

Paroxysmal sympathetic hyperactivity was first described by Penfield in 1929, who termed this condition as "diencephalic autonomic seizures" and hypothesized them to be caused by epileptiform discharges in the thalamic nucleus in raised intracranial pressure response to the irritation caused by raised intracranial pressure (ICP).[2] More than thirty different terms have been used to describe this condition, for example, paroxysmal sympathetic storms, autonomic storms, autonomic dysfunction syndrome, paroxysmal autonomic instability with dystonia, fever of central origin, and acute midbrain disorder, etc.[3]

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In 2014, a 26-member working group gave a consensus definition, laid down the diagnostic criteria, and recommended the use of the term "PSH" over others.[3] The diagnostic tool, paroxysmal sympathetic hyperactivity-assessment measure (PSH-AM), has two components, "diagnostic likelihood tool (DLT)" assessing the probability of diagnosis, and "clinical feature scale (CFS)" assessing the severity of clinical symptoms. The total score gives the probability of having the diagnosis. Farias–Moeller et al. defined PSH in children in their study as episodes of at least four of the following eight features: Tachycardia, hypertension, tachypnea, encephalopathy, muscle rigidity, hyperthermia, diaphoresis, and mydriasis.[1]

The reported prevalence of PSH among adults is 7.7–33% among intensive care unit (ICU) admissions, 8–25% after traumatic

brain injury (TBI), and 6–29% after non-TBI.[4–10] The prevalence of PSH in the pediatric population has been reported around 13–14% after brain injury.[5] However, there is a paucity of prospective pediatric data. Delayed diagnosis leads to unnecessary investigations, prolonged ICU stay, and increased treatment costs. Also, uncontrolled symptoms may further augment brain injury.

This study was planned to determine the incidence of PSH and to analyze its association with age, Glasgow coma scale (GCS), and outcome in children requiring neurocritical care.

## Materials and Methods

This was a prospective cross-sectional study conducted in the PICU of a tertiary care hospital in New Delhi, India from February to December 2016. Children admitted with neurocritical illness, for example, TBI, acute meningoencephalitis, space-occupying lesion, tubercular meningitis (TBM), stroke, peripheral neuropathy etc. were included in the study. The children who were diagnosed with brain death after initial resuscitation in PICU were excluded. The study was approved by the institutional ethical committee.

### Definition

Paroxysmal sympathetic hyperactivity is defined as having episodes of at least 4 out of 8 clinical features (tachycardia, hypertension, tachypnea, reduced level of consciousness, muscle rigidity, hyperthermia, diaphoresis, and pupillary dilation) which were not explained by other causes (sepsis, brain herniation, pain, medication overdose, or withdrawal) and persisted for at least three consecutive days.[1] Patients who had less than four of the aforementioned features with similar unexplained, paroxysmal episodes were also included as "incomplete PSH" and were analyzed separately.

### Data Collection

The demographic data such as age and gender; clinical characteristics such as diagnosis, clinical features of PSH, need for mechanical ventilation, duration of PICU stay and ventilation, and GCS at admission were recorded. The PRISM III score was calculated within 24 hours of admission. The outcome was recorded as improvement or death.

### Outcome Variables

The primary outcome variable was the incidence of PSH among children with neurocritical illnesses. The secondary outcome was the association of PSH with mortality and morbidities such as the requirement of mechanical ventilation, duration of PICU stay, and ventilation. Association with age, GCS, and severity of illness PRISM III was also analyzed. The patients who fulfilled less than four criteria for PSH were also analyzed separately for the above variables. Standard workup for sepsis by leucocyte counts, CRP, procalcitonin, and cultures was done to rule out sepsis before labeling as PSH and also episodic nature of symptoms with normal periods in between was an indicator of PSH.

### Statistical Analysis

The data was analyzed using IBM SPSS statistics software for Windows, version 20.0 (SPSS 20) (Armonk, NY: IBM Corp) and $p < 0.05$ was taken as significant. Mean/Standard deviation (SD) and median/Interquartile range (IQR) were used for normally and non-normally distributed descriptive data respectively. Chi-squared test was used for the comparison of categorical variables. For the comparison of categorical with quantitative variable, the Student's *t*-test and Mann–Whitney U tests were used respectively for normally and non-normally distributed data.

## Results

During the study period, 243 patients were admitted to the PICU. Fifty-four (22%) of them required neurocritical care and were included in the study (Flowchart 1). There were almost equal numbers of males and females, and half of them were above 5 years (Table 1).

Mechanical ventilation was required in 37 (62.9%) patients with a median duration of 14 (6, 24) days. The median duration of a PICU stay was 15.5 (5, 30) days. The central nervous system was primarily involved in 44 (81.5%) patients while 10 (18.5%) had peripheral nervous system involvement (Table 1). The diagnostic profile of the included patients is enlisted in Table 1.

Five (9.2%) patients had at least four features fulfilling the criteria for diagnosis of PSH. Out of these, four patients had meningoencephalitis (two viral, one bacterial, and one tubercular) and one had Guillain Barre Syndrome (GBS). The incidence of PSH among patients with meningoencephalitis was 17.4%.

Additionally, 30 (55.5%) patients who had less than 4 features of PSH were also analyzed (incomplete PSH). Out of these, 12 (40%) had three, 11 (36.7%) had two, and 7 (23.3%) showed only 1 out of 8 listed features.

The mean duration of PSH was 26 days and the mean number of episodes per patient was 116 while the frequency was lower among those with incomplete PSH. The most commonly observed feature was tachycardia followed by tachypnea, diaphoresis, and abnormal pupillary reaction (Table 2).

Patients who fulfilled all 4 criteria for PSH had significantly longer mechanical ventilation and PICU stay ($p = 0.038$ and

**Flowchart 1:** Flowchart of the study participants

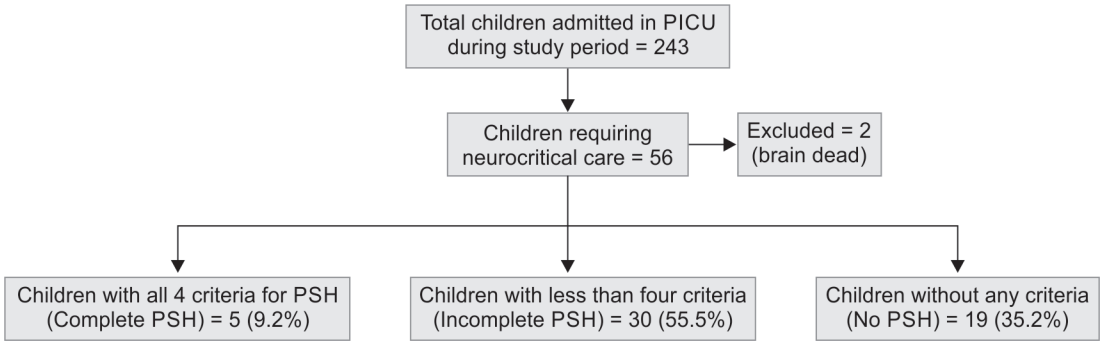

**Table 1:** Demographic and diagnostic profile of the study population ($N = 54$)

| *Parameter* | *Value* |
|---|---|
| Male:Female | 1:1 |
| Age | |
| <1 year | 11 (20.3%) |
| 1–5 years | 16 (29.6%) |
| >5 years | 27 (50%) |
| Duration of stay (Median/ Q1,Q3) | 15.5 days (5, 30) |
| Duration of ventilation (Median/Q1, Q3) | 14 days (6, 24) |

| *Diagnosis (54)* | *Complete PSH (n = 5) (%)* | *Three criteria (n = 12) (%)* | *Two criteria (n = 11) (%)* | *One criterion (n = 7) (%)* | *No criteria (n = 19) (%)* |
|---|---|---|---|---|---|
| **Central nervous system – 44 (81.5%)** | | | | | |
| Viral meningoencephalitis | 2 (40) | 3 (25) | 1 (9) | 3 (42.8) | 2 (10.5) |
| Bacterial meningitis | 1 (20) | 1 (8.3) | 0 | 0 | 3 (15.8) |
| TBM | 1 (20) | 1 (8.3) | 0 | 1 (14.2) | 0 |
| TBI | 0 | 1 (8.3) | 0 | 0 | 0 |
| Stroke | 0 | 1 (8.3) | 0 | 0 | 0 |
| Inborn error of metabolism | 0 | 1 (8.3) | 0 | 0 | 1 (5.3) |
| Enteric encephalopathy | 0 | 0 | 2 (18.1) | 0 | 1 (5.3) |
| Neurocysticercosis | 0 | 0 | 1 (9) | 0 | 0 |
| Metabolic encephalopathy | 0 | 0 | 1 (9) | 0 | 0 |
| Intracranial tumors | 0 | 0 | 1 (9) | 0 | 2 (10.5) |
| Acute encephalomyelitis | 0 | 0 | 1 (9) | 0 | 0 |
| Brain abscess | 0 | 0 | 0 | 1 (14.2) | 1 (5.3) |
| Hepatic encephalopathy | 0 | 0 | 0 | 1 (14.2) | 0 |
| Dengue encephalopathy | 0 | 0 | 0 | 0 | 3 (15.8) |
| Seizure disorder | 0 | 0 | 0 | 0 | 2 (10.5) |
| Transverse myelitis | 0 | 0 | 0 | 0 | 1 (5.3) |
| Hypoxic brain injury | 0 | 0 | 0 | 0 | 1 (5.3) |
| Meningomyelocoele | 0 | 0 | 0 | 0 | 1 (5.3) |
| Uremic encephalopathy | 0 | 0 | 0 | 0 | 1 (5.3) |
| **Peripheral nervous system – 10 (18.5%)** | | | | | |
| GBS | 1 (20) | 2 (16.6) | 2 (18.1) | 0 | 0 |
| Postdiphtheritic polyneuropathy | 0 | 2 (16.6) | 2 (18.1) | 1 (14.2) | 0 |
| **Total ($n = 54$) (%)** | **5 (9.2)** | **12 (22.2)** | **11 (20.4)** | **7 (13)** | **19 (35.2)** |

GBS, Guillain-Barre syndrome

**Table 2:** Characteristics of the PSH episodes

| *Number of features of PSH* | *Duration mean (days)* | *Number of episodes/ patient* | *Tachy cardia* | *Hypertension* | *Tachypnea* | *Temperature* | *Diaphoresis* | *Muscle rigidity* | *Pupils* |
|---|---|---|---|---|---|---|---|---|---|
| Four or above criteria (5) | 26 | 116 | 5 (100%) | 2 (40%) | 2 (40%) | 3 (60%) | 2 (40%) | 2 (40%) | 4 (80%) |
| Three criteria (12) | 11.7 | 51.5 | 12 (100%) | 3 (25%) | 0 | 1 (8.1%) | 3 (25%) | 3 (25%) | 10 (81.7%) |
| Two criteria (11) | 10.6 | 29.6 | 10 (91%) | 1 (9.9%) | 0 | 0 | 1 (9.9%) | 0 | 9 (81.8%) |
| One criterion (7) | 8.1 | 17.2 | 3 (42.%) | 0 | 1 (14.3%) | 0 | 1 (14.3%) | 0 | 1 (14.3%) |

**Table 3:** Comparison of clinical characteristics of patients with and without PSH

| | *All criteria (n = 5)* | *Not meeting all criteria (n = 49)* | *p-value* |
|---|---|---|---|
| Age (months) | | | |
| Mean (SD) | 45.4 (44.5) | 57.9 (34.9) | 0.51 |
| Median (IQR) | 36 (10–72) | 60 (24–84) | |
| Sex (male%) | 4 (80%) | 24 (48.9%) | 0.18 |
| Ventilated | 3 (60%) | 34 (69.3%) | 0.67 |
| Duration of ventilation (days) | | | |
| Median (IQR) | 39 (28–58.5) | 12 (5.5–22) | **0.038** |
| Duration of stay (days) | | | |
| Median (IQR) | 39 (28–58.5) | 12 (5–27) | **0.013** |
| GCS at admission | | | |
| Mean (SD) | 8.4 (4.67) | 9.78 (5.36) | 0.584 |
| PRISM III | | | |
| Mean (SD) | 10.6 (6.9) | 4.8 (4.42) | **0.011** |
| Mortality | 2 (40%) | 16 (32.6%) | 0.74 |

IQR, interquartile range; SD, standard deviation

$p = 0.013$, respectively), and also had higher PRISM III scores ($p = 0.011$) compared to those who did not. Patients who showed any feature of PSH had significantly longer PICU stay and ventilation requirements ($p = 0.002$ and $p = 0.001$, respectively). There was no significant difference in the age or GCS at admission (Table 3).

Thirty patients improved and were discharged while 24 did not improve (18 died and 6 were discharged against advice), however, the mortality was similar in all the groups (Table 3).

## Discussion

We analyzed the incidence and associations of PSH in children requiring neurocritical care. A total of 9.2% of children developed features of PSH which were similar to an adult study by Fernandez–Ortega et al.[6,7] Kirk et al.[5] also found a similar incidence of PSH in children with TBI (9.7%) while the incidence in those with anoxic brain injury was higher (30.8%).[5] Incidence of PSH among patients with meningoencephalitis was 17.4% in our study. This was lower than the incidence reported by Farias–Moeller et al. who used the same criteria for diagnosis.[1] Rabinstein et al. studied adult patients in neurological ICU and found that the incidence of PSH was 33% in patients with TBI while it occurred in only 6% of those with other neurological diagnoses, for example, intracranial hemorrhage or hypoxic brain injury.[11] Their findings support the lower incidence of PSH in our study as only one patient had TBI.

Most of the studies on PSH have been conducted in patients with TBI whereas TBI is uncommon in pediatric ICU. The difference in incidence from our study may be due to different patient populations and different criteria used for diagnosis. By using PSH-AM criteria in adults with TBI, Samuel et al. found that 69% of them had either possible or probable PSH with a sensitivity of 94% and a specificity of 35%.[12] Perkes et al. showed that most of the reported cases in adult literature are due to TBI (79%) followed by hypoxic insult (9.7%) and stroke (5.4%).[13] Although TBI constitutes the major proportion of adults with PSH, a higher proportion of TBI admitted in adult ICUs may be a reason for this observation.[4]

Paroxysmal sympathetic hyperactivity is associated with various conditions, for example, TBI, hypoxic brain injury, GBS, botulism, meningoencephalitis, autoimmune encephalitis, Japanese encephalitis, TBM, neuronal ceroid lipofuscinosis, cerebrovascular thrombosis, and moyamoya disease.[1,14–21] Farias–Moeller et al. showed that the incidence of PSH was higher among those with non-bacterial causes compared to bacterial meningoencephalitis.[1] In our series, five patients had PSH, of those, four patients had viral meningoencephalitis and one had GBS.

We used the criteria laid down by Farias–Moeller et al. for the diagnosis of PSH.[1] There is wide variation in the diagnostic criterion in the literature regarding the number of criteria needed for making a diagnosis; the range of deviation needed in the parameters and the timing of assessment.[13] The PSH-AM tool given by the consensus group is for adults and the pediatric version of the scale has not been developed and validated yet.[3] Although Pozzi et al. and Alofisan et al. have modified it in their own way (both using different values for clinical parameters) for pediatrics and used it, this is not validated or by consensus of any group.[22–24] Some other people have used cluster of symptoms without applying any scale/criteria.[25,26] In addition, the number of episodes and the number of days for which episodes persisted also varied in different studies. However, most of the authors agree that all the features may not be present in all patients.

Based on this literature, we also analyzed patients with less than four criteria of PSH, and we named it "incomplete PSH." We found that a significant number of patients had at least one feature of PSH episodically. Those included a variety of diagnoses including neurocysticercosis, intracranial tumors, intracranial bleeding, neuropathy, hepatic encephalopathy, enteric encephalopathy, and acute demyelinating encephalomyelitis. There was a significant association of the poorer outcome (consistent association between longer duration of ventilation and duration of PICU stay) even with the presence of a lesser number of features pertaining to PSH. Although it cannot be concluded as to whether the poorer outcome is due to PSH or PSH is due to the greater severity of the underlying disease in these children. Patients with three features of PSH (but not those with one or two features) also had significantly higher admission PRISM scores as compared to those who did not have PSH.

Hinson et al. found that elevated temperature during the first 24 hours was suggestive of the occurrence of PSH.[8] Farias–Moeller et al. also showed that fever upon presentation was significantly higher among those with PSH.[1] Kirk et al. showed

that hypertension, diaphoresis, and dystonia were the most important predictors of PSH with a combined area under a curve of 0.92.[5] In our study, all the patients with complete feature of PSH had tachycardia (100%), followed by pupillary abnormality and hyperthermia (60%). Among the patients with any feature of PSH (including incomplete PSH), tachycardia was the most common symptom followed by tachypnea and pupillary abnormality. Also, in our study, PSH lasted for a mean duration of 26 days, and the mean number of episodes per patient was 116 which was similar to that reported by Fernandez–Ortega et al.[6]

We found that the patients with PSH had a longer duration of PICU stay and ventilation. The finding was similar to other studies.[5–7,24] We did not find any difference in the gender distribution and age among those with or without PSH. Fernandez–Ortega et al. reported that the patients with PSH were younger and males were more likely to develop PSH, similar findings were reported by Pozzi et al.[6,22]

Patients with complete features of PSH had higher severity scores PRISM III. We could not find any study in the available literature using PRISM III for severity assessment. Fernandez–Ortega et al. used the acute physiology and chronic health evaluation score (APACHE) score among adult patients with or without PSH and did not find any difference in the groups.[7]

In our study, GCS at admission or discharge was not associated with the occurrence of PSH. Fernandez–Ortega et al. had similar observations regarding GCS at admission, but they found that GCS score at discharge was poorer among those with PSH.[6,7] The patients with PSH were found to have lower chances of discharge to home and had a poorer cognitive outcome.[5] Alofisan et al. found poor functional outcomes in survivors of TBI with PSH than survivors without PSH.[24] Pozzi et al. found that the patients with PSH had higher mortality.[22] We did not find any significant difference in the mortality of the patients with or without PSH. Long-term cognitive outcome was not assessed in our study.

The strength of our study was the prospective design, inclusion of varied diagnoses, and that we also analyzed the patients with less than four criteria for PSH. The limitations of the study were the small sample size and lack of follow-up. Diagnosis of PSH is a limitation in the absence of uniform standard criteria available for children. Multicentric studies with larger sample sizes are required to further evaluate the clinical associations and long-term outcomes of PSH in children. The PSH-AM criteria need to be validated in pediatric population.

## Conclusion

The study showed that the incidence of PSH in children requiring neurocritical care was 9.2%. Occurrence of PSH was associated with longer PICU stay and prolonged ventilation requirement and was also associated with poorer severity scores. Glasgow coma scale at admission, age, and gender were not associated with the occurrence of PSH. Although this does not clarify whether PSH is the cause of poor outcomes or the result of greater disease severity.

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