Incidence of Paroxysmal Sympathetic Hyperactivity after Traumatic Brain Injury in a Tertiary Care ICU: A Retrospective Cohort Study

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Abstract

Background Paroxysmal sympathetic hyperactivity (PSH**)** is an understudied complication of traumatic brain injury (TBI). PSH usually presents with transient rise in sympathetic outflow, leading to increased blood pressure, heart rate, temperature, respiratory rate, sweating, and posturing activity. We retrospectively analyzed the incidence of PSH in TBI using PSH-assessment measure (PSH-AM) scale.

Methods This single-center retrospective cohort study was conducted in traumatic head injury patients admitted in the intensive care unit from January 1, 2016 to December 31, 2019 in a tertiary care center. The data was collected from the hospital database after obtaining approval from the hospital ethics committee.

Results A total of 287 patients (18–65 years of age) were admitted to intensive care unit (ICU) with TBI out of which 227 patients were analyzed who had ICU stay for more than 14 days. PSH was diagnosed in 70 (30.8%) patients. Mean age of PSH positive patients was 40 ± 18 and 49 ± 11 years for PSH negative patients ($p < 0.001$). The age group between 40 and 50 years had a higher incidence of PSH. The age and Glasgow coma score (GCS) were significantly associated with the occurrence of PSH. The GCS score demonstrated good accuracy for predicting the occurrence of PSH with AUC 0.83, 95% CI of 0.775 to 0.886, and a *p*-value of 0.001.

Conclusion We observed that the incidence of PSH was 30.8% in the patients with TBI. Age and GCS were found to have a significant association for predicting the occurrence of PSH. The patients who developed PSH had a longer length of hospital stay in ICU.

Keywords
- dysautonomia
- frontal lobe contusion
- traumatic brain injury
- Glasgow Coma Scale

Introduction

Paroxysmal sympathetic hyperactivity (PSH) is an understudied complication of traumatic brain injury (TBI). PSH usually presents with a transient increase in sympathetic outflow, leading to a rise in blood pressure, heart rate, temperature, respiratory rate, sweating, and posturing activity, which may also persist over time.[1] Although the association between PSH and patients outcomes after TBI is not well defined, the objective quantification of PSH may be associated with global patient outcomes.[2] Penfield[3] studied autonomic instability which he called "diencephalic autonomic epilepsy" as early as in 1929. There appears to be a disparity between the combined involvement of both parasympathetic and sympathetic nervous systems in Penfield's original case of diencephalic autonomic epilepsy and the dominant characterization of

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the condition as involving sympathetic hyperactivity alone as it appears in the recent literature.[1,2]

The "PSH syndrome" caused by the autonomic dysfunction, was first reported in 2010.[4,5] Later on, an expert group in 2014 proposed a diagnostic criteria for the syndrome.[1] PSH is seen more commonly in patients with TBI than the other central nervous system pathologies such as anoxic brain injury, stroke, tumors, infections, and in some other intracranial pathologies.[6] In the last few years, approximately 80% cases of PSH have been reported following TBI.[7,8] The wide range of the incidence of PSH in TBI (8–33%) suggests that current diagnostic criteria may underestimate the disease.[9-11] Studies have reported that PSH in TBI patients was associated with worse clinical outcomes and longer ICU stay.[11,12] However, some studies have found that PSH was not an independent predictor for the increased morbidity or poor clinical outcome.[4,8,13]

Several intracranial pathologies, such as seizures, hydrocephalus, and hypoxia, invariably have overlapping manifestations with PSH. Hence, under-recognition and misdiagnosis frequently occur in clinical practice.[9,14,15] The present study aimed to highlight a common but less frequently diagnosed complication of TBI. The primary objective of this study was to find the incidence of PSH after TBI using PSH assessment measure (PSH-AM) scale by Baguley et al.[1]

Methods

This was a single-center, retrospective cohort study in patients with TBI admitted to the intensive care unit (ICU) of a tertiary care center between January 1st, 2016 and December 31st, 2019. The study protocol was reviewed and approved by the hospital Ethics Committee. The patients' demographic profile and Glasgow coma scale (GCS) were recorded from admission records. Patients between 18 and 65 years of age who were admitted to ICU were included in the study. The patients with a length of ICU stay <14 days, diabetes, coronary artery disease, hypertension, and chronic obstructive pulmonary disease were excluded from the study. The data of symptoms starting from ICU admission to until discharge or death for a minimum of 14 days during hospitalization was collected from the institutional record registers and compiled using the proposed assessment tools to determine PSH occurrence. Computed tomography (CT) findings were recorded using the Marshall score.[16]

PSH-AM scale has two components, including "diagnosis likelihood tool" (DLT) and "clinical feature scale" (CFS). DLT was derived from 11 clinical characteristics, and a score of 1 was assigned to each feature (► **Supplementary Appendix A**, available in the online version). CFS gave points according to the severity of symptoms from 0 to 3 (► **Supplementary Appendix B**, available in the online version). PSH was considered unlikely in the patients where a combined total score was less than 8, possible if the score was 8 to 16, and probable if the score was >16.

Statistical Analysis

The data was analyzed using the statistical software SPSS (version 20). Descriptive statistics were expressed as percentage for the categorical variables, while mean and standard deviation were calculated for continuous variables. Comparison of data between patients with PSH^+ and PSH^- was done using Mann-Whitney U test for continuous variables and Chi-square test for categorical variables. The *p*-value of <0.05 was considered as significant. Multiple logistic regression was performed for variables showing significant correlation. Results were expressed as odds ratio (OR). Receiver operating characteristic curve (ROC) analysis was performed to determine the predictive level of GCS score for PSH positive patients.

Results

A total of 287 patients with TBI were screened, out of which, 227 patients were analyzed. Amongst these, 121 (53.3%) patients were male and 106 (46.7%) patients were female. Out of the 227 patients, 70 (30.8%) patients satisfied the diagnostic criteria for PSH and were categorized as PSH positive, and the remaining 157 (69.2%) patients were PSH negative (►**Table 1**). Among the PSH positive patients, 48 (68.6%) patients had PSH-AM scores between 8 and 16 (possible), and 22 patients had PSH-AM score more than or equal to 17 (probable).

A comparison of various parameters between PSH positive and PSH negative patients is depicted in ►**Table 2**. PSH positive patients had a significantly lower age (40 ± 9 vs. 49 ± 8, $p < 0.001$) and GCS upon admission (9 ± 2 vs. 12 ± 2; $p < 0.001$). Intracranial lesions and distribution of PSH in each lesion are depicted in ►**Table 3**. Patients with frontal lobe contusion were more likely to be PSH positive with a *p*-value of <0.001. The average length of ICU stay was significantly longer in PSH positive cases (27 ± 4 days) as compared with PSH negative patients (21 ± 2 days) with a *p*-value of <0.001. Mortality of PSH positive cases was 12/70 cases (17%) as compared with PSH negative, which was 19/157 cases (12%). Although mortality was higher in PSH positive group, but the difference was not statistically significant ($p = 0.3$). Marshall score on admission showed no significant difference between the groups.

Predictors for the Occurrence of PSH in TBI Patients

The multiple logistic regression analysis showed that age, GCS, and length of hospital had significant association with PSH occurrence. An odds stay ratio of 0.35 and 95% CI of 0.23 to 0.54 for GCS indicate that with the increase in GCS, the chance of PSH occurrence decreases by 0.65 times

Table 1 Clinical characteristics of patients

Total number of patients	227
Age (years)	46.2 ± 9.8
Males	121 (53.3)
Females	106 (46.7)
GCS	11.09 ± 2.4
Cranial surgery	60 (26.4)
Mortality	31 (13.6)

Abbreviations: GCS, Glasgow coma scale; SD, standard deviation.
Note: The data is represented as n (%), mean+SD.

Table 2 Comparison between PSH +ve and PSH–ve patients

Variables	PSH (+) *n* = 70	PSH (–) *n* = 157	*p*-Value
Age (years)	40 ± 18	49 ± 11	**<0.001**[a]
GCS on admission	9 ± 2	12 ± 2	**<0.001**[a]
Cranial surgery	21	39	0.400
Marshall score on CT scan	2 ± 1	2 ± 1	0.186
Length of stay (in days)	**27**± **4**	**21**± **2**	**<0.001**
Mortality *n* (%)	12/70(17)	19/157(12)	0.30

Abbreviations: CT, computed tomography; GCS, Glasgow coma score; SD, standard deviation.
Note: Data are presented either as number and percentage or Mean ± SD.
[a]*p*< 0.05 was considered as significant.

Table 3 Type of brain injuries

Contusions	PSH(+)	PSH(–)	*P*-Value
Frontal contusion	45	35	**<0.001**[a]
Parietal contusion	11	11	1.000
Temporal contusion	23	48	0.819
Occipital contusion	5	12	0.600
Both side contusion	32	59	0.900
Brain stem contusion	11	27	0.770
Subcortical (diencephalon, thalamus, basal ganglia)	34	71	0.700
Cerebellar contusions	2	5	0.890
Other intracranial lesions			
Intraventricular hemorrhage	14	25	0.450
Diffuse axonal injury	14	30	0.870
Hydrocephalous	3	7	0.950
Extradural hematoma	14	27	0.620
Left extradural hematoma	9	13	0.280
Right extradural hematoma	5	14	0.650
Subdural hematoma	23	48	0.820

Note: CT evaluation in study patients showed that many patients had more than one positive CT findings.
[a]*p*-Value < 0.05 considered significant.

Table 4 Multiple logistic regression analysis of risk factors correlated to paroxysmal sympathetic hyperactivity

Variables	Beta-coefficients	*p*-Value	Odds ratio	95% Confidence interval
Age	−0.088	0.010[a]	0.916	0.857–0.979
GCS (Admission)	−1.030	<0.001[a]	0.357	0.236–0.541
Frontal contusions	2.031	0.52	7.622	0.985–58.995
Length of stay	0.585	<0.001[a]	1.796	1.431–2.253

Abbreviation: GCS, Glasgow coma scale.
[a]*p*-Value <0.05 is significant.

(i.e., 65% reduced chance of PSH positivity). With an increase in one-unit score of GCS, the chances of PSH occurrence decreased by 3% (Beta-coefficient = −1.030). On ROC analysis, the GCS score demonstrated an area under the ROC curve (AUC) of 0.83, suggesting good accuracy of GCS for predicting PSH. The highest cut-off value for GCS was 12.50, with a sensitivity of 94.3 and 58% specificity. Below this GCS, the patient has a probability of being PSH positive. The odds ratio for a frontal contusion is 7.6, which indicates these patients have 7.6 times higher risk of developing PSH, but the 95% CI is 0.985 to 58.995, which shows a low precision.

Similarly, an odds ratio of 0.91 and 95% CI of 0.85 to 0.97 for the age indicates as the age increases, the chance of occurrence of PSH decreases by 9% (►**Table 4**).

Discussion

A considerable number of theories exist as to the pathophysiology of PSH. Epileptiform discharges in the diencephalon are a potential cause for PSH.[3] These discharges can be identified using electroencephalography. There are two theories behind PSH onset, disconnection theory, and

inhibitory-excitatory ratio model. Disconnection theory deals with inhibitory pathways being ablated or malfunctioning post-injury, which leads to sympathetic pathways from the cortical and subcortical areas being less controlled, resulting in a "sympathetic storm." Excitatory-inhibitory models suggest that lesions in the mesencephalic area decrease the inhibition pathways from the brain. This may lead to pathways that are usually non-nociceptive, being sensed as nociceptive, and this results in the peripheral sympathetic nervous system overactivity.[1]

In the present study, PSH was diagnosed in 30.8% patients (70/227) with TBI during the study period utilizing the PSH-AM scale. Perkes et al.[4] found approximately 80% of PSH cases following TBI, 10% in post anoxic brain injury, 5% in stroke, and the remaining 5% in hydrocephalus, tumor, hypoglycemia, infections, and unspecified causes. The higher incidence reported in TBI may be because this condition has been studied extensively in brain trauma patients as TBI constitutes the most common cause of brain insult as a cause of admission to ICU. One series of neurocritical care patients reported an incidence of 33% in post-TBI patients and 6% due to other causes of brain injury.[17] Regardless of underlying diagnosis, the reported incidence rates in various studies from several countries range from 8 to 33%.[7,8,17-20] The range reflects differences in population, diagnostic criteria, and time period of examination.[8] Also, higher incidence seen in younger age group is because they have stronger autonomic activity compared with older age group. One study in patients after TBI showed that 92% had evidence of autonomic hyperactivation within the first week. According to the consensus recommendation published in 2014, a minimum of 14 days of patient care are necessary to observe symptoms and to allow time for the clinicians to rule out all other potential differential diagnoses.[1] At 1 week, 24% of patients had autonomic hyperactivity and at 2 weeks only 8% met the criteria for dysautonomia. Hence, we included the patients who stayed for more than 2 weeks in ICU.[8] The rates of PSH may be changing over time. The present study has demonstrated a relatively high incidence of PSH (30.8%) even after 14 days of ICU admission and contributed to significant mortality and morbidity.

CT studies have suggested that certain types of lesions might be associated with the symptoms of PSH. The most commonly listed injuries in studies are: extradural hematoma, subdural hematoma, and other focal space-occupying lesions.[11,17] However, some studies have reported localized or diffuse lesions as the causes for this syndrome.[21-23] The prognostic value of individual CT variables, such as the location of injuries and types of intracranial lesions, has been evaluated (►**Table 4**). Most patients in the present study had more than one CT finding, depicted in ►**Table 4**. The patients with a frontal cortical contusion were having a significant association with PSH occurrence. In our study, the patients with normal CT scan but low GCS were presumed to have diffuse axonal injury and were not subjected to MRI as per institutional protocol.

MRI is superior to CT for detecting lesions in those areas of the brain which may be important for the development of PSH, namely, the corpus callosum, deep nuclei, and brainstem.[24,25] Recent MRI studies have shown evidence that injury to the deep brain structures, periventricular white matter, corpus callosum, diencephalon, or brainstem seems to be associated with the development of PSH, suggesting the importance of diffuse axonal injury as a causative agent.[17,23] Patients with PSH have an increased number of lesions in the dorsolateral aspect of the midbrain and upper pons compared with the number of lesions in the cortex, subcortex, corpus callosum, and diencephalon.[17,26]

The central autonomic network is complex involving the cerebral cortex (the insular and medial prefrontal regions), amygdala, stria terminalis, hypothalamus, and brainstem centers (periaqueductal gray, parabrachial pons, the nucleus of the tractus solitarius, and intermediate reticular zone of the medulla).[27] The relationship between the brain's prefrontal cortex and heart has been studied, and the amygdala is believed to be a major efferent source of modulation of autonomic, endocrine, and cardiovascular responses.[28] This may be the reason for a higher incidence of PSH in cases of frontal cortical contusions.

In concordance with previous studies, our study too has shown that PSH patients have longer period of stay in hospital.[13,29,30] Mathew et al[31] concluded that the presence of PSH in patients with severe TBI was associated with a prolonged hospital stay, more deaths, and unfavorable outcome. Patients often are more vulnerable to infections and spend longer times on ventilators, which can lead to an increased risk of various lung diseases.[30] PSH also increases the amount of time it takes a patient to recover from injury, compared with patients with similar injuries who do not develop PSH episodes. It often takes patients who develop PSH longer to reach similar levels of the brain activity seen in patients who do not develop PSH.

There are few limitations to the current study, including retrospective nature and single-center data. Also, the study population were not evaluated with MRI which could have given additional information on pathophysiology of PSH. We believe that large multicenter studies are required to determine various factors that may predict the PSH occurrence and affect the outcomes of patients with TBI.

Conclusion

TBI was associated with high incidence of PSH. We observed the incidence of PSH following TBI as 30.8%. Lower GCS, younger age, and frontal contusion were the main predisposing factors. However, PSH did not influence the mortality but increased the length of hospital stay. The higher GCS was associated with lesser chances of PSH occurrence. The length of ICU stay was significantly higher in patients with PSH.

Conflict of Interest

None declared.

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