

A Study of Cardiac Autonomic Dysfunction in Patients with Traumatic Brain Injury

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Abstract: Background: Traumatic brain injury (TBI) is a leading cause of disability worldwide. Autonomic dysfunction presents clinically as Paroxysms of Autonomic Instability with Dystonia (PAID) and sub-clinically Heart Rate Variability abnormalities. This is a treatable contributor to secondary brain damage and disability after TBI. Objectives: To describe prevalence of clinical and subclinical cardiac autonomic dysfunction in patients with TBI and to look for its association with severity of brain injury and functional status. Methods: This was a cross sectional, observational descriptive study conducted on in-patient basis. Adult patients with TBI underwent the study. History, examination, functional assessment using Modified Barthel Index (MBI), Disability Rating Scale (DRS) and Glasgow Outcome Scale Extended (GOS - E) were recorded. Primary outcome measures were screening for PAID and Heart rate variability (HRV) measurement. Results: Among the 12 patients who underwent the study, 5 (41.67%) were noted to have PAID. All 5 belonged to severe TBI subgroup. On HRV assessment, in addition to the patients who had PAID, 4 patients were noted to have at least one parameter suggestive of sympathetic hyperactivity. Conclusion: The prevalence of PAID in TBI patients was found to higher than previous studies. This may be due to the increased number of severe TBI patients recruited for the study. Even in the absence of clinically evident dysautonomia, subclinical autonomic dysfunction is very common. This study hints at autonomic dysfunction to be a common, under-diagnosed sequela to TBI that could point towards a treatable cause of reduced functional recovery.

Keywords (MeSH): PAID (Paroxysmal Autonomic Instability with Dystonia); Dysautonomia; Heart rate variability; Brain Injury, Traumatic; Autonomic dysfunction.

1. Introduction

Traumatic brain injury (TBI) is a form of acquired brain injury resulting from a trauma ranging from simple blow to the head to a penetrating injury of the brain. The most common mechanisms of TBI are motor vehicle related injuries, falls and assaults.

Impairments secondary to a TBI may be motor, psychological, cognitive, or autonomic. Autonomic dysregulation secondary to TBI may result from direct trauma to areas involved in regulation of the Autonomic nervous system (ANS). Areas such as the hypothalamus, nucleus tractus solitarius (NTS), medulla, and the subfornical organ (SFO) contribute to overall control of the ANS; injury to any one of them could result in autonomic dysregulation.¹

Autonomic dysfunction in TBI is a significant pathophysiological mechanism that can lead to a worsened quality of life. The presence of autonomic dysfunction has also been shown to correlate with increased morbidity and mortality in moderate and severe TBI.²

Dysautonomia or autonomic dysfunction should be managed aggressively as there are good reasons to believe that lack of diagnosis and under management contributes to unnecessary morbidity. In particular, core temperatures above 38–39°C produce neuronal death in various animal models of brain

injury.^{3, 4} These temperatures are present in 68% of people following severe TBI⁵ whereas mean maximal temperatures in dysautonomic subjects remain above this level for longer than 2 weeks.⁶ The higher metabolic demands of posturing patients,⁷ and prolonged abnormalities of gastrointestinal tract function,⁸ result in a highly catabolic state producing an estimated 25% loss of body weight.⁶ The resulting malnourishment places the patient at a higher risk of critical illness myopathy or neuropathy.

In addition to significant mortality and morbidity, PAID has also been associated with reduced functional recovery during the sub-acute and chronic phase during rehabilitation. Functional independence, quality of life and return to work has been correlated with autonomic dysfunction.

Once diagnosed in the acute setting, adverse consequences can be avoided by early treatment. Current treatment is aimed at mitigating signs and symptoms to decrease adverse events such as cardiac hypertrophy, dehydration, muscle wasting, contractures and delayed recovery which contribute to increased morbidity. Current pharmacological options include bromocriptine, alpha agonists such as clonidine, baclofen, gabapentin, opiates, non-selective beta-blockers and HBOT has been recently tried as a second line modality.
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Early initiation of symptom - specific therapy is thought to decrease complication rates and ICU length of stay and to facilitate recovery.¹⁶ Understanding both the cause and complexity of these storming events will lead to improved therapeutic interventions.

Although studied across various patient populations including TBI and stroke, evaluation of autonomic dysfunction has not been done in the Indian context. Despite western studies attempting associating presence of autonomic dysfunction and functional outcomes, the results have been inconsistent and inconclusive.

This study goes a step further and attempts to find abnormalities in autonomic function at the subclinical level using resting HRV measurement. HRV is the variation in time intervals between adjacent heart beats. This variability helps cope with the uncertain and changing environment of the body. An optimal level of HRV is associated with better self - regulatory capacity, and adaptability.

This study attempts to throw light at a potentially under diagnosed, treatable contributor to secondary brain damage and how specific subsets of TBI may be at more risk of developing autonomic dysfunction in the acute and sub - acute phase of recovery.

2. Methods

A cross sectional descriptive observational study was conducted in patients with TBI admitted under the Department of Physical Medicine and Rehabilitation (PMR), during the period from December 2018 to September 2020. Institutional ethical clearance was procured before the commencement of the study.

Patients who had a single traumatic event to the brain of ages ranging from 18 to 60 were recruited for the study after at least 2 weeks of the event. Patients with pre - existing cardiovascular, pulmonary and thyroid conditions, or those taking medications affecting the autonomic nervous system (including beta blockers, alpha agonists) were excluded from the study. Patients that were haemodynamically unstable or with active infection after the TBI were also excluded.

Once enrolled and written consent given, their demographic details, and clinico - radiographic findings were documented. Initial GCS, duration since event and presence of seizures was also recorded.

Relevant investigations were done to rule out other differential diagnoses and confounding factors, such as TSH, Total leucocyte count, Urine R/M and Chest X - ray were also noted.

Monitoring of vitals was done during the stay in the ward. Periodic spontaneous increase in body temperature, heart rate, blood pressure, respiratory rate, excessive sweating, agitation, and dystonia (or posturing) were looked for. 5 of the above 7 features presenting simultaneously, presenting episodically, extending for more than 3 days were considered as PAID.

The frequency and duration of such episodes of autonomic dysfunction were recorded. Once other differential diagnoses of malignant hyperthermia and Serotonin syndrome along with infective pathology were ruled out, the diagnosis of PAID was confirmed. The management of the same was based on the Department protocol. Non - selective beta blocker such as Propranolol was given with a starting dose of 5 mg twice daily, which was titrated based on clinical response.

Each subject also underwent 15 - minute resting awake Heart rate variability (HRV) measurement at the institutional clinical Physiology lab. Both time domain and frequency domain parameters were assessed.

Frequency domain analysis shows how much of the ECG signal lies within one or more frequency bands (ranges). The bands used in this study are Low frequency (LF), high frequency (HF) bands and the ratio between LF/HF. Although LF is affected by both sympathetic and parasympathetic activity, HF is more specific to vagal activation. LF/HF is generally considered to be an estimate of ratio between sympathetic nervous system (SNS) and parasympathetic nervous system (PNS).¹⁷

The time domain indices are numbers that can be obtained from statistical analysis of interval between heart beats. Commonly used commonly are NN interval, which is the interval between adjacent QRS complexes. Calculated values from NN interval include SDNN, pNN50 and rMSSD. SDNN is the standard deviation of NN intervals measured in milliseconds (ms). PNN50 is the percentage of successive differences of intervals between normal heart beats > 50 ms. rMSSD is the Root mean square of successive differences of normal - to - normal intervals in ms.

The functional scores for the enrolled patients were also recorded based on application of scales and clinical interview with patients and primary caregivers. Modified Barthel index (MBI), Disability rating scale (DRS) and Glasgow Outcome Scale Extended (GOSE) were used.

A data entry proforma was used to document the data. All the data was entered into a Microsoft Excel spreadsheet. STATA statistical analysis software Version 16 was used for analysis of the data. All categorical data was summarized using frequency and percentages, and all continuous data was described using mean and standard deviation (SD). P - value was considered significant at 5% level of significance for all comparisons. Fisher's exact test was used to look for association between 2 variables.

3. Results

During the study period, 54 patients were screened for the study. 12 patients were included in the study after fulfilling the criteria. Most frequent causes of exclusion were uncontrolled hypertension, uncontrolled diabetes and prior history of medications that may affect the autonomic nervous system.

Patient characteristics

Among the 12 patients selected, all were males. They had an average age of 37.75, with SD of 15.1. It ranged from 21 to 60. The TBI incident had happened on an average 3.6 weeks prior to assessment, with a SD of 1.95. Most common mode of injury was Road traffic accidents (RTA) (83.3%), followed by fall from height (16.7%). Most subjects had a poor initial GCS in the first 24 hours, and hence belonged to severe TBI subgroup (83.3%). 1 patient each belonged to mild and moderate category (8.3%).

Functional outcome measures

On clinical interview with subject and primary evaluation, mBI, DRS and GOSE were applied to all subjects. ThemBI scores ranged from 0 to 87, the average score was 45.91 ± 39.14. Disability rating scale was applied on all 12 patients. The DRS scores ranged from 0 to 12, with a mean score of 9.23±3.64. Although majority of the patients were severe TBI, generally low DRS scores were noted on evaluation during rehabilitation period. On evaluation through Glasgow coma outcome scale, all patients were found to be either moderately or severely disabled. 9 out of 12 were severely disabled (75%) and 3 out of 12 were moderately disabled (25%).

Paroxysmal Autonomic Instability with Dystonia (PAID)

Episodes of PAID were noticed in 5 patients (42%). The frequency of such episodes ranged from 4 times a day to 6 times a day with an average of 5 episodes per day. A single episode lasted 23±6.7 minutes, ranging from 15 minutes to 30 minutes. All 5 patients were treated medically as per Department protocol. 4 among the 5 patients (80%) were given Tab. Propranolol 20 mg per day in 2 divided doses. 1 patient (20%) was given Tab. Clonidine 0.2 mg per day in 2 divided doses.

HRV measurement

On assessing the data obtained from measuring 15 - minute resting HRV, it was found that even patients who did not have episodes of PAID had abnormal HRV. Data suggestive of sympathetic over activity was considered abnormal in both frequency and time domain parameters.

Frequency domains such as HF (%), LF (%) and LF/HF ratio were looked at. LF ranged from 22.24 to 99.6%, with an average of 59.8%. LF was found to be abnormally high in 5 of the 7 subjects without PAID episodes. HF ranged from 4.3% to 70.28%, with a mean of 42.75%. Since HF is suggestive of vagal tone, low HF was considered abnormal and was found in 2 patients who were clinically asymptomatic.

LF/HF ratio ranged from 0.32 to 25.14, with an average ratio of 6.18. Since LF/HF ratio is considered equivalent to SNS/PNS, an abnormal increase was suggestive of sympathetic over activity. Such over activity was noted in 2 apparently normal subjects.

At least one frequency domain variable was indicative of sympathetic hyperactivity in all 7 patients who did not show PAID episodes clinically (100%).

Time domain variables considered were rMSSD (ms) and pRR50 (%). The average rMSSD was 74.25 ms and it ranged from 6.28 ms to 401.6 ms. It was found to be abnormally low in 2 patients who were clinically asymptomatic. The mean pRR50 was 12.46 % ranging from 0 to 44.76%. pRR50 was found abnormally low in 3 clinically normal subjects suggestive of sympathetic over activity.

At least one time domain variable was indicative of sympathetic hyperactivity in 3 patients who did not show PAID episodes clinically (42.8%).

3 patients had both time domain and frequency domain parameters suggestive of sympathetic hyperactivity (28.6%).

Tests of Association

Association between presence of PAID and severity of brain injury was tested using Fischer's exact test. No significant association could be established (p=0.424), although majority of the patients who had PAID belonged to severe brain injury group. (Table 1)

Fischer's exact test was done to look for presence of PAID and functional scales. No significant association was found. All p values were greater than 0.05; mBI (p=0.308) (Table 2), DRS (p=0.219) (Table 3) or GOSE (p=0.539) (Table 4).

4. Discussion

Autonomic dysfunction manifesting as PAID is a fairly common complication of acquired brain injury found in the acute and sub - acute phase during rehabilitation. This study tries to examine the prevalence of cardiac autonomic dysfunction, clinically evaluated as Paroxysms of Autonomic Instability with Dystonia in patients with traumatic brain injury. The findings from this study showed 42% patients had PAID, which is to a certain extent higher than previously reported prevalence of 33% by Zheng et al in 2020¹⁸. This could be explained by the over - representation of severe TBI patients recruited for this study.

This study also evaluated subclinical autonomic function testing through HRV measurement. It was found that among the 7 patients who did not show symptomatic PAID, at least one parameter showed abnormally high sympathetic activity in 4 patients, with 2 of them having both time and frequency domain variables abnormal.

This represents a potentially undiagnosed patient group with autonomic dysfunction, who may be at a risk of longer duration of post traumatic amnesia, longer duration of hospital stay, and greater healthcare cost¹⁹. Abnormal HRV can also be a marker for increased risk of developing arrhythmias, myocardial ischemia or infarction.²⁰

It was also found that no significant association exists between presence of clinical features of cardiac autonomic dysfunction, manifesting as PAID and severity of the injury based on initial GCS. Although a study by Lv et al in 2010 showed admission GCS score was significantly correlated with occurrence of dysautonomia after brain injury, on multivariate logistic regression, it was found that there was

no independent association between dysautonomia and admission GCS score¹⁵.

In this study, no significant association could be established between presence of PAID and functional outcome measures such as Modified Barthel Index, Glasgow outcome scale extended and Disability Rating Scale. A study done by Hendricks et al²¹ showed that although patients who had dysautonomia were noted to have lower GOSE scores, there was no statistically significant difference in the scores between patients who had dysautonomia and the ones that did not.

Another study by Sara Laxe et al²² also attempted to show association between functional outcome and presence of autonomic dysfunction in brain injury patients. The study showed no significant association between presence of dysautonomia and outcome scales such as FIM, GOSE and DRS.

5. Conclusion

This study was designed to evaluate the prevalence and pattern of autonomic dysfunction clinically presenting as PAID in patients with traumatic brain injury during the subacute period in the Indian context.

Based on the findings of this study, it is noted that PAID has a prevalence of 42% among traumatic brain injury patients, which warrants timely evaluation and treatment. Most patients had 4 to 6 episodes daily, each lasting 15 to 30 minutes. Propranolol and Clonidine were effective modes of treatment of the same. PAID was found to more prevalent in patients with severe traumatic brain injury although no significant association could be established. There was no association found between functional outcome measures and presence of PAID.

HRV abnormalities are much more common than clinically evident PAID episodes. Patients after a TBI, especially a severe injury may undergo screening with HRV measurements to further individualize and plan the neurorehabilitation program. Caregivers and the patient may be sensitized regarding increased risk of cardiac complications in such patients and danger signs to look for.

From the perspective of neuro - rehabilitation, cardiac autonomic dysfunction needs to be routinely looked for and diagnosed early. Treatment of clinically evident PAID with a multi - drug approach may be appropriate, as it can prolong the hospital duration and reduce the rehabilitation potential of the patient, resulting in poor end goal attainment as well as increased financial and caregiver burden.¹⁹

This is one of the first studies in the Indian scenario which looked at both clinical and subclinical autonomic dysfunction and its effect on functional outcomes in the acute and sub - acute setting.

Further multi - centre studies with larger sample sizes are recommended with a focus on the effect of autonomic dysfunction in long term recovery and functional status of traumatic brain injury patients are suggested. HRV data

could be refined by using 24 - hour Holter monitoring, as well as HRV measurement during specific activity.

Conflict of interest

No conflict of interest to declare

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Table 2: Association between PAID and MBI scores

MBI ² score	PAID ³ present	PAID absent	Total
0 - 10	2 (100%)	0 (0%)	2 (100%)
11 - 20	0 (0%)	2 (100%)	2 (100%)
21 - 30	1 (50%)	1 (50%)	2 (100%)
31 - 40	0 (0%)	0 (0%)	0 (0%)
41 - 50	0 (0%)	0 (0%)	0 (0%)
51 - 60	0 (0%)	0 (0%)	0 (0%)
61 - 70	0 (0%)	0 (0%)	0 (0%)
71 - 80	1 (50%)	1 (50%)	2 (100%)
81 - 90	1 (25%)	3 (75%)	4 (100%)
91 - 100	0 (0%)	0 (0%)	0 (0%)
Total	5 (41.67)	7 (58.33%)	12 (100%)

2 - *MBI – Modified Barthel Index

3 - *PAID – Paroxysmal Autonomic Instability with Dystonia

Table 3: Association between PAID and DRS scores

DRS ⁴	PAID ⁵ present	PAID absent	Total
0 - 5	2 (28.57%)	5 (71.43%)	7 (100%)
6 - 10	3 (75%)	1 (25%)	4 (100%)
11 - 15	0 (0%)	1 (100%)	1 (100%)
16 - 20	0 (0%)	0 (0%)	0 (0%)
21 - 25	0 (0%)	0 (0%)	0 (0%)
26 - 29	0 (0%)	0 (0%)	0 (0%)
Total	5 (42.67%)	7 (58.33%)	26 (100%)

4 - *DRS – Disability Rating Scale

5 - *PAID – Paroxysmal Autonomic Instability

Table 4: Association between PAID and GOSE scores

GOSE ⁶	PAID ⁷ present	PAID absent	Total
Dead	0 (0%)	0 (0%)	0 (0%)
VS	0 (0%)	0 (0%)	0 (0%)
SD -	3 (60%)	2 (40%)	5 (100%)
SD +	1 (25%)	3 (75%)	4 (100%)
MD -	1 (33.33%)	2 (66.67%)	3 (100%)
MD+	0 (0%)	0 (0%)	0 (0%)
Good recovery	0 (0%)	0 (0%)	0 (0%)
Total	5 (41.67%)	7 (58.3%)	12 (100%)

6 - *GOSE – Glasgow Outcome Scale – Extended

7 - *PAID – Paroxysmal Autonomic Instability

Tables

Table 1: Association between presence of PAID and severity of TBI

Severity of injury	PAID ¹ present	PAID absent	Total
Mild	0 (0%)	1 (100%)	1 (100%)
Moderate	0 (0%)	1 (100%)	1 (100%)
Severe	5 (50%)	5 (50%)	10 (100%)
Total	5 (41.67%)	7 (58.33%)	12 (100%)

1- *PAID – Paroxysmal Autonomic Instability with Dystonia