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Autonomic dysfunction presenting as postural tachycardia syndrome following traumatic brain injury

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Abstract

Background: *Autonomic dysregulation (also called diencephalic epilepsy) has been reported following traumatic brain injuries (TBI). However, until now, postural tachycardia syndrome (POTS) has not been reported as a long-term complication in patients who have suffered a TBI. We report on a series of patients who developed POTS after suffering TBI.*

Methods: *Eight patients who were referred to our center had suffered TBI and developed features of orthostatic intolerance following head trauma. The patients' neurological, neurosurgical and autonomic data (charts and/or physician letters) were then carefully reviewed for demographic characteristics, comorbid conditions, symptoms of orthostatic intolerance, medications and response to medication. These patients were diagnosed as having POTS, primarily based on their clinical features and findings from the head-up tilt test (HUTT). The data presented is observational and descriptive (percentages or means).*

Results: *Eight patients (seven of them women) aged 21–41 years had suffered from TBI and had developed features of POTS. All had been normal with no symptoms prior to their TBI. All patients experienced orthostatic dizziness, fatigue, palpitations and near syncope. Six patients suffered from frank syncope. Six patients developed significant cognitive dysfunction, and three developed a chronic pain syndrome following trauma. All of the patients reported severe limitations to their daily activities and had been unable to keep their jobs, and two were housebound. Six patients demonstrated a good response to therapy with various combinations of medication. The symptoms of orthostatic intolerance and syncope improved with the initiation of medical therapy, as well as their reported quality of life. Two patients failed to show any improvement with various combinations of medications and tilt training, and continued to experience orthostatic difficulties.*

Conclusions: *Postural tachycardia syndrome may, in some cases, be a late complication of traumatic brain injury.* (Cardiol J 2010; 17, 5: 482–487)

Key words: postural tachycardia syndrome, trauma, brain injury

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Introduction

Traumatic brain injury (TBI) is a significant cause of both mortality and permanent disability each year in the United States. Nearly 1.4 million people suffer from TBI in the United States annually [1]. Approximately 20% of all TBI cases occur as a consequence of motor vehicle accidents (the principal reason for hospitalization in TBI patients) [2–4]. In addition to the well-documented effects that TBI has on the somatic nervous system, traumatic injury may affect the autonomic nervous system as well. Autonomic dysfunction after TBI may manifest itself in disturbances in heart rate, respiratory rate, temperature regulation or sweating. Some patients may also experience muscle spasticity as well as abnormal posturing. These problems have been called 'diencephalic epilepsy' and sympathetic storms [5, 6]. The exact incidence of autonomic dysfunction following TBI is unknown. However, of patients admitted to an intensive care unit following TBI, the reported incidence of autonomic dysfunction ranges anywhere from 8% to 33% [5, 6]. Symptoms of autonomic dysregulation in TBI have been reported in the period immediately following injury or in the early phases of recovery, with few reports of long-term effects. Postural tachycardia syndrome (POTS) is a subtype of autonomic dysregulation characterized by an excessive pooling of blood in the lower extremities. Thus far, POTS has not been reported as a long-term complication in patients who have suffered from TBI. We report a review of a group of patients who developed POTS as a long-term complication of TBI.

Methods

The study was a retrospective descriptive analysis of patients followed up at the University of Toledo Medical Center. Our Institutional Review Board approved the study. Patients were included in this study if they developed POTS following a head trauma. These patients were managed at different places for orthostatic symptoms; all of them had suffered TBI in the past. They were seen in our clinic primarily for a second opinion regarding diagnosis and management options. These patients were diagnosed as having POTS primarily based on their history, clinical features and findings from head upright tilt table testing (HUTT).

Criterion for diagnosis of POTS

Postural orthostatic tachycardia is defined as symptoms of orthostatic intolerance (of greater than six months duration) accompanied by a heart rate increase of at least 30 beats/min (or a rate that exceeds 120 beats/min) that occurs in the first ten minutes of upright posture or HUTT occurring in the absence of other chronic debilitating disorders. Symptoms include: fatigue, orthostatic palpitations, exercise intolerance, lightheadedness, diminished concentration, headache, near syncope and syncope [7–12].

HUTT protocol

The protocol used for tilt table testing has been described elsewhere, but basically our testing consisted of a 70-degree baseline upright tilt for a period of 30 minutes, during which heart rate and blood pressure were monitored continually. If no symptoms occurred, the patient was lowered to the supine position and an intravenous infusion of isoproterenol started, with a dose sufficient to raise the heart rate to 20–25% above the resting value. Upright tilt was then repeated for a period of 15 minutes. Patients were included in the study if they had a POTS pattern on HUTT (rise in heart rate without any change in blood pressure) [7–12]. The treatment protocols employed were based on our previous experiences with orthostatic disorders and are described in detail elsewhere [7–12].

A total of eight patients who were referred to our center suffered TBI and developed features of orthostatic intolerance following head trauma. Patients' neurological, neurosurgical and autonomic data (charts and/or physician letters) were then carefully reviewed for demographic characteristics, comorbid conditions, symptoms of POTS, medications and response to medication. The time from the injury to the development of symptoms was also recorded. The data presented is observational and descriptive (percentages or means)

Results

Eight patients (seven women and a man, aged 21–41) were identified as having suffered TBI and subsequently developed POTS. Six of them were Caucasian. The results are summarized in Table 1.

Nature of injury

Seven patients suffered TBI in motor vehicular accidents and one patient suffered a closed head injury due to blunt trauma from a freight elevator. Two patients received brain and neck injury following motor vehicular accidents. Five patients suffered such severe closed head injuries (intracerebral hemorrhage) that they required admission to an intensive care unit.

Table 1. Clinical characteristics of patients with postural tachycardia syndrome (POTS) following traumatic brain injury.

Pt #	1	2	3	4	5	6	7	8
Age at onset of trauma	38	36	39	35	41	38	37	21
Time to onset of POTS	2 years	2 years	2 years	3 years	2 years	3 years	3 months	3 months
Sex	F	F	F	F	F	F	M	F
Race	NK	C	C	C	C	C	C	C
Type of trauma	MVA	MVA	MVA	MVA	Hit by freight elevator	MVA	MVA	MVA
Brain injury	Closed	Closed	Closed	Closed	Closed	Closed	Closed/ /neck	Closed/ /neck
ICU requirement	Yes	No	Yes	No	Yes	Yes	No	Yes
Syncope	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Near syncope	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Orthostatic palpitations	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dizziness	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Fatigue	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chronic pain syndrome	Yes	No	Yes	No	No	No	Yes	No
Cognitive dysfunction	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Medications:								
Beta-blockers	No	No	No	Yes	No	Yes	No	Yes
Pyridostigmine	No	Yes	Yes	No	No	No	No	Yes
Midodrine	Yes	No	Yes	No	Yes	Yes	Yes	No
Fludrocortisone	No	Yes	No	No	Yes	No	No	No
Modefinil	Yes	No	No	No	Yes	No	No	No
Cerefolin	Yes	No	Yes	No	Yes	Yes	Yes	Yes
SSRI	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Response to therapy	Good	Good	Good	Good	Poor	Poor	Good	Good

F — female; M — male; NK — not known; C — Caucassian; MVA — motor vehicular accidents; ICU — intensive care unit; SSRI — serotonin reuptake inhibitor

Onset of symptoms

The onset of orthostatic symptoms was insidious in each patient. There was no record of acute autonomic dysfunction recorded in any of the patients during their initial hospitalization. The time from TBI to the onset of symptoms of POTS (as recorded from the charts, physician letters and other communications) ranged from three months to three years. During this period (from TBI to onset of POTS symptoms), six patients had also developed cognitive dysfunction and three developed chronic pain syndrome.

All patients had recovered from their TBI and all were initially sent to rehabilitation centers. All patients successfully completed the acute rehabilitation programs, and each reported having resumed normal activities.

Symptoms of POTS

After a successful recovery from TBI, and completing an acute rehabilitation program. all eight patients later developed symptoms of orthostatic intolerance. The onset in each patient was slow and insidious. The time from TBI to onset of these symptoms as reported by the patients and in the physician letters and communications ranged from three months to three years. All patients reported that the episodes of orthostatic intolerance were frequent (two to four episodes over six months). The description of these episodes was similar in each patient. All patients experienced a cold-like sensation followed by feelings of extreme fatigue, lightheadedness, palpitations and presyncope while upright which was relieved by recumbency. Six patients developed frank syncope.

Each of these patients demonstrated a rise in pulse rate of > 30 bpm from sitting to standing position ($n = 5$) and an absolute rise in heart rate > 120 bpm ($n = 3$) within ten minutes of assuming an upright posture.

Head-up tilt test

All eight patients underwent HUTT. All patients demonstrated either an absolute heart rate

> 120 bpm or an increase by > 30 bpm within the first ten minutes of an upright tilt. There was a variable degree of fall in blood pressure associated with symptoms of orthostatic intolerance, similar to that reported during their spontaneous episodes. None of the patients had a resting heart rate > 100 bpm. We did not routinely evaluate catecholamine levels in any of these patients.

Activities of daily living

All patients reported having severe limitations in activities of daily living. In addition, each patient reported loss of employment, and two were completely housebound.

Management

Following recognition of POTS in these patients, they were treated with a variety of medications (Table 1). No drug is presently approved by the US Food and Drug Administration for the treatment of POTS, and the treatments listed here are all 'off label'.

The therapeutic management approach for these patients was based on our experience of the management of patients with POTS [8–13]. In patients suffering from the partial dysautonomic form of POTS, initial therapy is directed at augmenting fluid volume and increasing peripheral vascular resistance. To augment volume, we employ the mineral corticoid fludrocortisone acetate, starting at 0.1 to 0.2 mg per day. An alternative agent is desmopressin acetate 0.1 to 0.2 mg orally at bedtime. If needed, we then add a vasoconstrictor such as midodrine 5 mg orally three to four times daily. The dose may be slowly shifted up to 10 to 15 mg QID if necessary. As many patients are most symptomatic in the morning, we often advise that they take their first dose of midodrine 15 to 20 minutes before getting out of bed. If midodrine is effective but not tolerated, methylphenidate can be an effective alternative. In patients who are not responsive to, or intolerant of, the above-mentioned therapies, we often add either a serotonin reuptake inhibitor (SSRI) or a norepinephrine reuptake inhibitor. Whereas the SSRIs are more helpful in neurocardiogenic syncope, the norepinephrine reuptake inhibitors appear to be somewhat more useful in POTS. If an SSRI is used, those with a combined serotonin norepinephrine effect (duloxetine and venlafaxine) appear to work best. A promising new therapy is pyridostigmine (mestinon), an acetylcholinesterase inhibitor that is thought to facilitate ganglionic neural transmission in both the sympathetic and parasympathetic nerves [14]. The drug appears most effective in patients with post-viral POTS, as well as in those with POTS secondary to an autoimmune disorder (such as lupus or Sjögren syndrome). We usually start with a dose of 30 mg orally BID and titrate to 60 to 90 mg orally three times a day if necessary. In patients who are severely affected by POTS and in whom no other therapy is effective or tolerated, we use the drug erythropoietin. Although initially introduced to treat anemia, erythropoietin has been found to process potent vasoconstrictive effects with demonstrated utility in treating orthostatic disorders. Protocols for its use are given elsewhere [13]. The usual starting dose is 10 000 IU subcutaneously once weekly. Complete blood counts are monitored monthly to ensure that the hematocrit does not exceed 50%.

An additional therapy for refractory patients is the somatostatin analog octreotide, because of its potent vasoconstrictive effects. It is administered by subcutaneous injection beginning at 50 μg two to three times daily.

In the hyperadrenergic form of POTS, patients often respond best to agents that block norepinephrine or its effects. One agent that is particularly helpful is clonidine HCI in either pill or patch form. We start the oral form at 0.1 mg PO one to two times a day and filtrate upward. The patch form of clonidine is quite useful because it provides a constant and continuous amount of the drug for up to one week at a time. The combined alpha and beta blocking drugs labetalol and carvedilol are quite useful in some patients because pure beta blockers may exacerbate symptoms (because of unopposed alpha receptor stimulation). Methyldopa has been reported to be useful in some patients, as has phenobarbital. In addition, both the SSRIs and norepinephrine reuptake inhibitors are useful in select patients.

Six patients demonstrated a good response to therapy with various combinations of medications. The symptoms of orthostatic intolerance and syncope improved with initiation of medical therapy, as well as their reported quality of life. Two patients failed to show any improvement with various combinations of medications and tilt training, and continued to experience orthostatic difficulties.

Discussion

Disturbances of the autonomic nervous system (ANS) are well-recognized complications of TBI. In the acute period following TBI, autonomic dysfunction is manifested by a period of intense sympathetic hyperactivity, resulting in hypertension, fever, and tachycardia extensor posturing (dystonia) [14–17].

These symptoms often begin five to seven days after injury and may last anywhere from two weeks to several months. It is felt that this phase of the autonomic dysregulation occurs from injury to one or more aspects of the brain that normally control the autonomic nervous system. These areas potentially include the cortical aspects of the anterior temporal, insular and orbitofrontal regions that influence the hypothalamus.

Additionally damage to the subcortical areas of the nucleus tractus solitarious and the amygdala may also cause hypothalamic damage resulting in a state of autonomic dysregulation [18–21].

To date, there have been no reports of late aspects of autonomic dysfunction resulting in orthostatic intolerance following TBI. Postural tachycardia syndrome is a type of autonomic dysfunction syndrome usually manifested by excessive orthostatic blood pooling with a compensatory tachycardia. The usual definition of POTS is a greater than 30 beats/minute increase in heart rate (or a total of a rate of greater than 120 beats/min) that occur in the first ten minutes of upright posture not associated with other conditions that could simulate this effect, such as prolonged bed rest (greater than three months duration) [7–13].

The current study describes a group of patients who appear to have developed POTS as a late complication of TBI. None of the patients reported here had any symptoms of POTS prior to TBI. The other reported conditions that seem to provoke POTS, such as severe viral infections and pregnancy, were not present in any of the patients described in this series. The only event temporally related to the development of their POTS was the TBI. No patient in this series was reported to have developed acute autonomic dysregulation in the early phases following their injury. The clinical features of the group of patients described here with post-traumatic POTS appear for the most part identical to POTS patients in general. While the majority of patients in our study improved with therapy, two patients have continued to suffer disabling symptoms despite all treatment attempts. At this point, it is unclear why patients who have suffered from a TBI would develop POTS, or if their long-term outcomes will be different from other POTS patients in general. Close follow-up of these patients over time will help clarify this.

Limitations of the study

Our study was limited by the fact that it was a single center, retrospective observational study of a small group of patients. The information on symptoms and their severity was based on patient reporting as recorded from the patient charts and physician communications. Another limitation of the current study is that the catecholamine levels were not checked. The response to the therapy was not objectively measured with a HUTT; rather, therapy was assessed by patient-reported symptoms and clinical observation. The estimation of the time from TBI to onset of symptoms was determined from patient interviews and referring physicians' communications and would be limited by a recall bias. Also, no other markers of autonomic dysfunction were evaluated in this small group of patients.

Despite all these limitations, the reported series of patients had a common pattern of TBI followed by later symptoms of orthostatic intolerance. A prospectively designed study following patients who suffer from TBI may provide a better insight into unresolved issues that this report could not address.

Conclusions

Postural tachycardia syndrome may, in some cases, be a late complication of traumatic brain injury.

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