Paroxysmal Sympathetic Hyperactivity in TBI: Unanswered Questions

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Abstract

Traumatic brain injury (TBI) is a complex management condition. Mild to moderate presentation is dealt with mostly in a non-ICU setting, while severe TBI ends up in intensive care units. The presentation and course of severe TBI is a team effort, and attempts are made to prevent complications and reduce morbidity. One condition which is still not clear and usually presents after initial stabilization is sympathetic overactivity. Here we will try to go over unanswered questions about this condition. We do not believe that the suggested answers to these questions are all set in stone and will change as we have a better understanding.

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Traumatic brain injury is a complex management condition. Mild to moderate presentation is dealt with mostly in a non-ICU setting, while severe TBI ends up in intensive care units (ICU). The presentation and course of severe TBI is a team effort, and attempts are made to prevent complications and reduce morbidity. One condition which is still not clear and usually presents after initial stabilization is sympathetic overactivity. Here we will try to go over unanswered questions about this condition. We do not believe that the suggested answers to these questions are all set in stone and will change as we have a better understanding.

Is it a Condition or a True Disease?

Traumatic brain injury is the presentation and course for the disease for which sympathetic overactivity can be seen. This is sometimes accompanied by sedation/analgesia withdrawal once TBI stabilization. The key aspect is stable intracranial pressure, and no further neurosurgical intervention is required for the initial TBI. To better understand the pathophysiology, it can be considered a true disease rather than a condition of intensive care in the TBI population. Once we understand the concept of disease, we try to manage and treat the full spectrum of the disease. This leads to our next question about the name for this disease.

What is the Best Name for this Condition?

This condition has gone through different names and definitions. There is no name as it is not clear if it is a part of the original CNS condition or a standalone identity. Some of these names are autonomic storm, sympathetic storm, dysautonomia, dystonia with autonomic dysfunction, or diencephalic autonomic epilepsy.[1] The different names are due to a combination of signs seen with the presentation and no clear understanding of the full background of this condition. This has led to confusion and an approach to treatment. The international consensus for this condition labeled the name paroxysmal sympathetic hyperactivity (PSH) due to attributes of the periodic nature of sympathetic activity, which the consensus group labeled as hyperactive.[2] Though this leads to the question of hyperactive based upon what criteria and what happens in-between this activity. The proposed definition helps to develop further insight and research to answer more questions and design any further research studies.

How Frequently it is Recognized by Clinicians?

The most common population inflicted with this condition are young severe post-traumatic patients. Though it can be seen after middle artery strokes, intracranial hemorrhage, encephalitis, and post-anoxic brain-injured patients. ICU caring for high-intensity neurocritical care volume will see this more commonly; the actual prevalence is not clear. Different numbers (8–33%)[3] are present in the literature and might be done with the unclear diagnosis and confounding factor of unstable brain condition for which the patient is in the intensive care unit. The time of onset from the original injury, clinical criteria used, and diagnostic methods used to create a wide range in the prevalence rate. Another aspect of PSH is that patients are usually not awake and still comatose from the TBI, consistent with the original problem of severe central nervous system injury.

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Which Feature is the Cardinal Hallmark for PSH?

Clinical presentation is the key aspect of PSH. The diagnosis is made upon clinical symptoms and signs. The patient is usually comatose, and it is an early, subtle change in the sympathetic axis that alerts the clinician about the impending hyperactivity. Once the full hyperactivity is present, it is more obvious. There are repeated episodes of fever, tachycardia, diaphoresis, and posture change.[4] The most important feature is the aspect of sudden onset, as seizures can do the same and sometimes requires video encephalogram to confirm that seizures are not present. The aspect of dystonic posture can confuse bedside staff to treat PSH with antiseizure medication. Tachypnea is noted, and most of these episodes lead to full ventilator support. Hypocarbia is a byproduct if the minute ventilation is not controlled.[5]

What is the Prevalence in the TBI Population?

Severe TBI patients present with extensive injuries, brain contusion, skull fractures, intracranial hemorrhage, early signs of herniation, younger age, and require neurosurgical intervention. The care is usually taken care of in the level 1 trauma center. The prevalence of PSH in this group is higher care compared to anoxic brain injury, stroke, encephalitis, and varied acute neurological crisis. A number mentioned in the literature is close to one-third of the severe TBI patients. The actual prevalence is probably higher as severe TBI populations progress through different stages of care and move to a different levels of care.

Is the Pathophysiology Clearly Defined?

The underlying mechanism where sympathetic hyperactivity is sudden, systemic, and pronounced is clear. There are thoughts and suggestions that cortical injuries lead to the release of inhiation of the central sympathetic system leading to periodic firing. This can be in the hypothalamus, brain stem, and spinal cord. The peripheral stimulation leading to excessive sympathetic crisis points toward spinal cord release from the inhibition from the higher centers.[6] Further research in this aspect of PSH may help us to narrow down the pathophysiological aspects to prevent or reduce the intensity.

Either any Specific Central Nervous Lesions are Present?

Focal trauma or focal lesion is the case with PSH, unlike seizure disorder, where focal lesion might be the culprit. Severe TBI brain has either diffuse, multicompartment or extensive injury. The same can be said about full middle cerebral infarction, anoxic brain injury, and encephalitis. On the clinical course, severe TBI has low GCS and long intensive care stay. Investigation shows most TBI with PSH have diffuse axonal injury patterns,[7] brain stem injury, central gray matter, and corpus callosum. Henceforth, it is not clear that there is a specific lesion that is causing PSH. Further insight with higher functional resolution might narrow down the focus.

What are the Diagnostic Guidelines?

Diagnosis of PSH is clinical, and there are suggested guidelines and scales based on this concept. Standardization in clinical practice is difficult, and compliance is cumbersome. There are three tools proposed in the literature, although none of these are used routinely: PSH assessment measure, Diagnostic likelihood tool, and clinical feature scale.[8] The use of these tools help with the diagnosis for less experienced clinician dealing with this diagnosis and help with future research.

Is the Parasympathetic System Involved or Not?

No research and clinical data attribute any role of parasympathetic system involvement in PSH initiation, propagation, maintenance, and cessation. There is still a question if and when this part of the autonomic system goes into suppression, underdrive, or checked during an episode of PSH. Also, what happens when the PSH episode subsides and medications used to subside an episode go into effect. Young, healthy severe TBI patients with a high parasympathetic tone might be a good starting point to look into this part of the autonomic system during the PSH course.

Is there any Routine Testing?

As mentioned above, it is a purely clinical diagnosis with a response to treatment clarifying the diagnosis. Severe TBI patients can have other associated established and new neurological conditions which require testing. There are no clear directions on which test and when that test is to be used. An early screen electroencephalogram can rule out TBI-induced seizures, especially after the initial 7 days. Neuroimaging might show changes that are seen in severe TBI and PSH, though none of these are specific for PSH. Electrolytes abnormalities need correction like hypomagnesemia, hyponatremia, and hypocalcemia.

What are the Key Conditions among the Differential Diagnosis?

Severe TBI patients have multiple complex intensive care issues. Some of these conditions are life-threatening and require investigations. Clinical seizures, neurogenic central fever, acute post-TBI central infection, cerebral edema, herniation syndromes, and vascular compromise can be part of the course. It is prudent to mention here certain diagnoses which can present with PSH, and PSH is not clear till the diagnosis is confirmed and managed. The list is ever-expanding, including cerebral fat embolism,[9] acute leukemia,[10] acute disseminated encephalomyelitis,[11] and any central condition leading to fever. Another important and extensively reported condition that clinicians should consider is the neurological manifestation of SARS-CoV-2 infection.[12]

Is it a Treatable Condition?

The mainstay of the treatment is general care, prevention of any complications, respiratory compromise, and dehydration. There is no clear pathway to take, and usually, prevention attempts after episodes and reducing the intensity of an episode are the goals. Patients who are connected to a mechanical ventilator will hyperventilate in a spontaneous mode or assist mode leading to hypocarbia, further compromising including dehydration and central vasoconstriction. Intensive rehabilitation with full medical care is required at a center where it is routine to admit severe TBI patients. Treatment focus is on beta-blocker, GABA agonists, opioid agonist, central alpha-2 adrenergic receptor agonists, and dopamine D2 receptor agonist agents. It is still not clear if we can treat the disease vs keep the stable. Over time either patient will proceed to arousal and or stay in unresponsive wakefulness syndrome.

Is there any Specific Treatment?

The specific approach which controls PSH is pharmacological.[13] These agents stop the process vs prevent this crisis from occurring. Some of the agents do both. It is not clear which one to use as one number option for a specific patient. Most of the time, clinicians will choose one agent to treat and prevent. If failure is seen, the drug of choice is a different class of medication. There is a trend towards a combination of agents in ICU patients where both preventive and active treatment are together. Propranolol and Clonidine can do both, while morphine is for active treatment purposes. Agents like gabapentin, bromocriptine, baclofen, and dantrolene are used to prevent episodes from happening.

When is this Condition Considered Refractory?

Severe TBI and axonal injury can lead to refractory PSH, although the data is not clear. When does the condition refractory: In the intensive care unit, at the rehabilitation facility, or after discharge to a permanent destination. Usually, after exhaustive use of all preventive and suppressive medication, a stage comes where it can be labeled as refractory. Intrathecal baclofen has been proposed as an agent for this stage of the disease.[14] Further work is required, and a better definition of refractoriness is warranted.

Is the Prognosis is Worse due to the Severity of TBI or the Presence of this Condition on its Own?

The prognosis of severe TBI is worse in the short and long term with PSH. Though it is not clear if the underlying severity of TBI leads to the worst outcome with PSH, one of the manifestations of TBI or PSH itself worsens TBI outcome. Further work will be required to clarify the impact of PSH on the severe TBI population. Management is indeed complicated further with PSH in the TBI population with increased ICU, and hospital length stay.

In conclusion, PSH is a serious condition seen in the severe TBI population. There are multiple aspects of this condition where management goals are clear and will require further work. Intensivists and other care providers should be on guard for the above-mentioned limitation and approach this condition in a multidisciplinary fashion. Future studies should include multicenter registry, controlled trials, and regularly updated guidelines.

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