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REVIEW ARTICLE

Paroxysmal Sympathetic Hyperactivity: Clinical Features, Identification and Treatment

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ABSTRACT

Background: In individuals with severe traumatic brain damage, paroxysmal sympathetic hyperactivity episodes, also known as autonomic storms, are not unusual. Fever, tachycardia, hypertension, tachypnea, hyperhidrosis, and dystonic posture are some of their distinguishing features. The episodes could start on their own or be brought on by stimuli. Although their pathogenesis is yet unclear, their symptoms unmistakably point to the activation or disinhibition of sympathoexcitatory regions. These spells are frequently mistaken for seizures, which results in needless antiepileptic medication treatment. Adequate hydration, ruling out mimicking illnesses (infection, pulmonary embolism, hydrocephalus, epilepsy), providing efficient analgesics, and avoiding triggers when recognized are general guidelines for managing paroxysmal sympathetic hyperactivity. Pharmacologic medications that are most beneficial are morphine sulfate and non-selective β-blockers, such as propranolol. When treating refractory instances, intrathecal baclofen may be useful. Although their effectiveness is less constant, bromocriptine and clonidine can be beneficial for certain patients.

Conclusion: PSH is a quite common but generally ignored complication of acute diffuse or multifocal brain diseases. It is most commonly seen in young, unconscious individuals who have suffered a severe traumatic brain injury. Recurrent, abrupt episodes of tachycardia, tachypnea, hypertension, perspiration, and occasionally fever and dystonic posture are the hallmarks of the condition. There is a clinical diagnosis. Reducing any external stimuli that may cause the episodes and initiating preventive and abortion medications (such as intravenous morphine, gabapentin, propranolol, and clonidine) are also part of the treatment. Early and sufficient PSH treatment may lower the risk of subsequent issues such as muscle contractures, malnourishment, and dehydration.

Keywords: Paroxysmal sympathetic hyperactivity, Traumatic brain injury, Intensive care unit

INTRODUCTION

A subset of patients has simultaneous paroxysmal transitory elevations in sympathetic activity related to temperature, heart rate, blood pressure, breathing rate, sweating, and posturing. These episodes can also last for a longer period and are linked to worse outcomes. 2010 saw the first recommendation for paroxysmal sympathetic hyperactivity (PSH) as a unifying label for these syndromes, which are brought on by the dysregulation of the sympathetic nervous systems [1]. While PSH outbreaks have historically been

linked to patients with severe acquired brain injuries (Traumatic brain injury (TBI), anoxic brain injury, stroke, tumors, infections, or unknown causes), the prevalence of PSH following TBI (33% versus 6% after other causes) indicates that TBI is the most common underlying cause of PSH [2].

Furthermore, over the last ten years, it has been shown that 80% of PSH cases follow traumatic brain injury. According to Zheng et al. [3], the wide incidence rates of this condition, which range from 8 to 33% of PSH, indicate both misunderstandings regarding disease identification and underlying discrepancies in existing diagnostic and admission criteria.

Approximately 8–10% of TBI survivors experience this side effect. According to earlier research, PSH did not independently indicate higher morbidity or worse clinical outcomes. On the other hand, results from additional research have indicated that PSH diagnosis in TBI patients was linked to longer hospital stays (about an additional 14 days) and worse clinical outcomes, such as considerably lower motor scores and worse Glasgow outcome scale scores [4].

PSH never arises as a basic condition; rather, it always results from different kinds and intensities of brain traumas [5].

Pathophysiology of PSH:

Despite the lack of a clear understanding of the pathophysiologic foundation of PSH, theories based on the "disconnection theory" and the "excitation-inhibition ratio (EIR) model" are tentative (3). The EIR model proposed that inhibitory centers within the brainstem (the periaqueductal grey matter) were unable to modulate spinal cord excitatory sensory circuits, whereas the disconnection theory proposed a loss of inhibitory cortical centers control over caudal excitatory autonomic centers (figure 1) [6].

Presently, the EIR model—which characterizes PSH as a two-stage pathogenic process—is the widely recognized theory. According to Zheng et al. [3], excitation first results from the disconnection of descending inhibitory pathways, and paroxysm is then stopped by the recovery of inhibitory components.

According to the EIR paradigm, the central and/or spinal level is the source of motor and sympathetic hyperactivity, and TBI impairs the suppression of descending and afferent non-noxious input. This idea challenges the pathological interpretations that each person's unique allodynic inclination to the reaction is what causes a patient's differential response to mildly noxious or non-noxious stimuli [7].

It further believes that in patients with traumatic brain injuries, a paroxysm of sympathetic symptoms could be a reaction to a structural or functional impairment of the midbrain. Additionally, this concept explains why those who have less participation from the brainstem experience paroxysms that last shorter and regain upper-spinal inhibition much more easily [2].

Lately, abnormalities in neuroendocrine regulation found in the maladaptive response have shed light on the pathogenesis of PSH. According to Smith et al. [1], paroxysms in the neurotransmitter system are caused by unregulated adrenergic outflow, which raises the level of catecholamine in the blood. Studies reveal that levels of dopamine (D), adrenocorticotropic hormone (ACTH), epinephrine €, and norepinephrine (NE) rise dramatically during the paroxysm, but NE and D fall during the intermittent phase instead of ACTH and E. This is because, while E is virtually entirely sourced from the adrenal medulla, NE and D are caused by the sympathetic nervous system's heightened excitability [8].

Serum catecholamines typically increase by two to three times, while ACTH generally increases by approximately 40%. Stimulus-driven alterations in the neurotransmitter system emphasize how crucial it is to take the triggering event into account while doing pathogenetic research. In summary, the primary pathophysiological aspects are caused by the induction of paroxysm, an abrupt and heightened reaction that stems from the afferent stimulation of the sympathetic nervous system [3].

Clinical Features of PSH:

PSH is characterized by a range of symptoms that indicate increased sympathetic activity, such as dystonia, arterial hypertension, tachypnea, hyperthermia, widespread sweating, and aberrant motor activity (dystonia, muscle rigidity, extension) [9].

These clinical characteristics appear suddenly in periodic episodes, either on their own or in reaction to external stimuli such as pain, bathing, secretory aspiration, light, touch, or physical treatment [10].

While sympathetic hyperactivity may appear at any point during the duration of the underlying illness, it is typically identified following the first week, when profound sedoanalgesia is either reduced or ceases entirely. According to published research, most cases include a diagnosis made a week following the patient's hospitalization. The paroxysms

typically last 30 minutes and occur three to five times each day [9].

Sweating, tachycardia, and hypertension were observed in all 343 individuals. Thirteen (44.8%) patients experienced posturing, twenty-eight (96.6%) had tachypnea, and twenty-eight (82.8%) had hyperthermia. Thirteen (44.8%) of the patients exhibited each of the six PSH symptoms [5].

These symptoms are linked to a number of unanticipated effects, including a higher overall mortality rate, a longer recovery period, an increased risk of infection, and other unfavorable results. The primary symptoms of PSH are usually accompanied by certain unexpected comorbidities, such as immunodepression, weight loss, heterotopic ossification, and cardiac involvement [11].

According to Mathew et al. [5], there is a strong correlation between the quantity of symptoms and the final result, with more widespread manifestations being linked to a worse prognosis.

Identification of PSH:

PSH is a real neurological emergency that could go unnoticed if ignored. The diagnosis necessitates a high level of suspicion and is mostly established by ruling out other theories. High mortality-morbidity rates are linked to inadequate detection and treatment of the illness [5].

Given the strong clinical nature of PSH diagnosis, other conditions with similar clinical features such as sepsis, bacteremia, airway obstruction, hypoxia, severe hypercapnia, hypoglycemia, seizures, neurological deterioration (e.g., intracranial hypertension, bleeding, edema, hydrocephalus), pulmonary thromboembolism, thyroid storm, acute myocardial infarction, and central hyperthermia of unknown cause must be ruled out as potential causes of the condition [9].

PSH is diagnosed using the combination of the "clinical features severity" (CFS) score and the "diagnosis likelihood tool" (DLT) score; this combination is known as the PSH-AM (assessment measure) score table (1) because there is no confirmation test. [12].

Recent and past cases demonstrate that PSH-AM can be used to stratify the severity of PSH in addition to acting as a trustworthy diagnostic criterion. The method is useful in diagnosing PSH in various forms of brain damage and may dynamically track the evolution of each PSH patient's clinical status [4].

Meyfroidt et al. [13] defined the CFS as a score that evaluates the existence and severity of the clinical parameters and the DLT as a score that evaluates the features of the episodes (frequency, length, persistence over time, etc.).

Treatment of PSH:

Traditional views hold that obstacles to the development of PSH treatment are the following:

1) Insufficient understanding of brain regions.

2) No definite relationship between neurotransmitters or hormones and clinical symptoms.

3) Lack of standardized measures to assess the curative effect.

4) Insufficient evidence from clinical trials regarding the benefits of intervention for long-term outcomes [2].

The care of this issue has, however, advanced significantly with the aim of mitigating deleterious effects, avoiding the triggering event, and reducing excessive sympathetic nerve activity. Determining the necessity and urgency of which symptoms require priority processing is the initial stage before beginning treatment [7].

The many basic symptom categories associated with each PSH phase should then be identified. The most frequent issues that physicians deal with, by far, are how to use medication and additional treatment during the interval phase and whether to use supportive therapy during the rehabilitation stage [11].

Previous research indicates that patients with long-term conditions have a sympathetic positive feedback loop that is hard to break, which makes therapy even more challenging. Finally, it's critical to think about the best options for treatment cycle, route, and timing [15].

Pharmacological Treatment: Table (2)

Physicians understand that pharmaceutical therapies should be based on a thorough examination of the various symptom types and individual variations, and a variety of medications have been used to treat PSH. In clinical practice, the majority of patients need to be treated with a combination of medications that may complement each other in order to target various syndromes and either prevent or treat paroxysms [16].

Unfortunately, a brief historical summary based on subjective rather than objective information will be provided, as there is no treatment that is particularly beneficial for PSH or that can prevent a recurrence. Opioids and benzodiazepines, for instance, are often utilized drugs. The majority of opioids, gabapentin, benzodiazepines, and central α-agonists or β-antagonists are the first-choice medications; bromocriptine, which is frequently used in

pharmacological combinations, is the second choice [7].

However, prior research has indicated that medication regimens may be more successful in managing symptoms in PSH patients. Additionally, the therapeutic effects might be enhanced by rapidly identifying episodes, avoiding needless therapy for alternative illnesses, modifying dosage, or switching to a different medicine based on the disease's progression [4].

Three therapy techniques are available, taking into account the information presented above: symptom eradication, symptom prevention, and refractory treatment. As a result of their quick half-life and quick onset, drugs used to treat symptoms can end paroxysmal episodes right away. Due to their effectiveness in clinical settings, morphine and short-acting benzodiazepines were previously the preferred medications [1].

Medications aimed at preventing symptoms are used to lessen the frequency and severity of symptoms experienced by PSH patients. Numerous pharmacological classes have demonstrated remarkable effectiveness in clinical practice, including long-acting benzodiazepines, baclofen, gabapentin, α2-agonists, non-selective BBs, and bromocriptine [2].

Finally, if uncontrollable symptoms develop, an ongoing intravenous infusion of drugs like dexmedetomidine, benzodiazepines, opioids, or propofol may be administered until the symptoms go away. It is imperative that practitioners understand that combination therapy may be required to avoid recurrent outbreaks and that chronic symptoms that are challenging to control should be treated with prophylactic drugs first [11].

Non-pharmacological Treatment:

Certain non-pharmacological therapeutic approaches for PSH have been suggested by recent investigations. Modifying the surroundings is a crucial step before starting treatment. Patients with hyperthermia can benefit from daily care and room temperature control to provide a less stressful atmosphere [15].

Currently, early enteral feeding adoption and close observation of nutrition, hydration, and mineral supplements are critical components of nutrition management. In the meantime, a few concerns have surfaced in the therapeutic setting, including the complete integration of each person's dietary and hydration needs, TBI patients' tolerance during PSH development, and the degree to which calorie intake can make up for increased energy expenditure [4].

A Formula for Managing PSH in Patients with Traumatic Brain Injury:

Checking for a clear history of head injuries in the patient is the first step towards making a diagnosis. According to algorithm figure (2) [3], each patient's medical data, including vital signs, nursing notes, and other clinical notes, are examined.

CONCLUSION

PSH is a quite common but generally ignored complication of acute diffuse or multifocal brain diseases. It is most commonly seen in young, unconscious individuals who have suffered a severe traumatic brain injury. Recurrent, abrupt episodes of tachycardia, tachypnea, hypertension, perspiration, and occasionally fever and dystonic posture are the hallmarks of the condition. There is a clinical diagnosis. Reducing any external stimuli that may cause the episodes and initiating preventive and abortion medications (such as intravenous morphine, gabapentin, propranolol, and clonidine) are also part of the treatment. Early and sufficient PSH treatment may lower the risk of subsequent issues such as muscle contractures, malnourishment, and dehydration.

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Consent for publication

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Competing interests

The authors declare that they have no competing interest.s

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Table (1): Paroxysmal sympathetic hyperactivity (PSH)-assessment measure [14].

Clinical Features Severity scale (CFS)					
	0	**1**	**2**	**3**	**Score**
HR	<100	100–119	120–139	>140	
RR	<18	18–23	24–29	>30	
SBP	<140	140–159	160–179	>180	
Temperature	<37	37–37.9	38–38.9	>39	
Perspiration	Null	Mild	Moderate	Severe	
Postures	Null	Mild	Moderate	Severe	
				CSF subtotal	
Severity of the clinical presentation				Null	0
				Mild	1–6
				Moderate	7–12
				Severe	>13
Diagnosis Likelihood Tool (DLT)					
The simultaneity of the clinical manifestations					
Paroxysmal presentation					
Sympathetic hyperactivity in response to non-painful stimuli					
Persistence of the clinical manifestations ≥3 consecutive days					
Persistence of the clinical manifestations ≥2 weeks post-injury					
Persistence of the clinical manifestations despite treatment of alternative diagnoses					
Treatment for reducing features of sympathetic hyperactivity					
≥2 daily episodes					
Absence of parasympathetic clinical manifestations during the episode					
The absence of other causes explaining the clinical manifestations					
History of acquired brain damage					
DLT subtotal (1 point for each clinical presentation)					
Combination total (CFS+DLT)					
Probability of diagnosis of PSH				Improbable	<8
				Possible	8–16
				Probable	>17

Table 2: Medications Used for Treatment of Paroxysmal Sympathetic Hyperactivity (PSH) [17].

Medication	Location of Action	Proposed Mechanism	Symptoms Treated
Baclofen	Centrally	$GABA_B$ agonist	Pain, clonus, rigidity
Benzodiazepines	Centrally	$GABA_A$ agonist	Agitation, hypertension, tachycardia, posturing
Bromocriptine	Centrally at hypothalamus	Dopamine agonist	Dystonia, fever, posturing
Clonidine	Centrally decreased sympathetic outflow	α_2 agonist	Hypertension
Dantrolene	Peripherally	Calcium ion blocker	Muscle rigidity, posturing
Dexmedetomidine	Centrally	α_2 agonist	Hypertension, agitation, tachycardia
Gabapentin	Centrally	GABA agonist	Spasticity, allodynic response
Intrathecal baclofen	Centrally	$GABA_B$ agonist	Pain, clonus, rigidity
Morphine	Centrally medullary vagal nuclei and peripherally	μ-opiate agonist	Tachycardia, peripheral vasodilation, allodynic response
Propranolol	Peripherally decreasing effect of catecholamine	β-blocker	Hypertension, tachycardia, fever

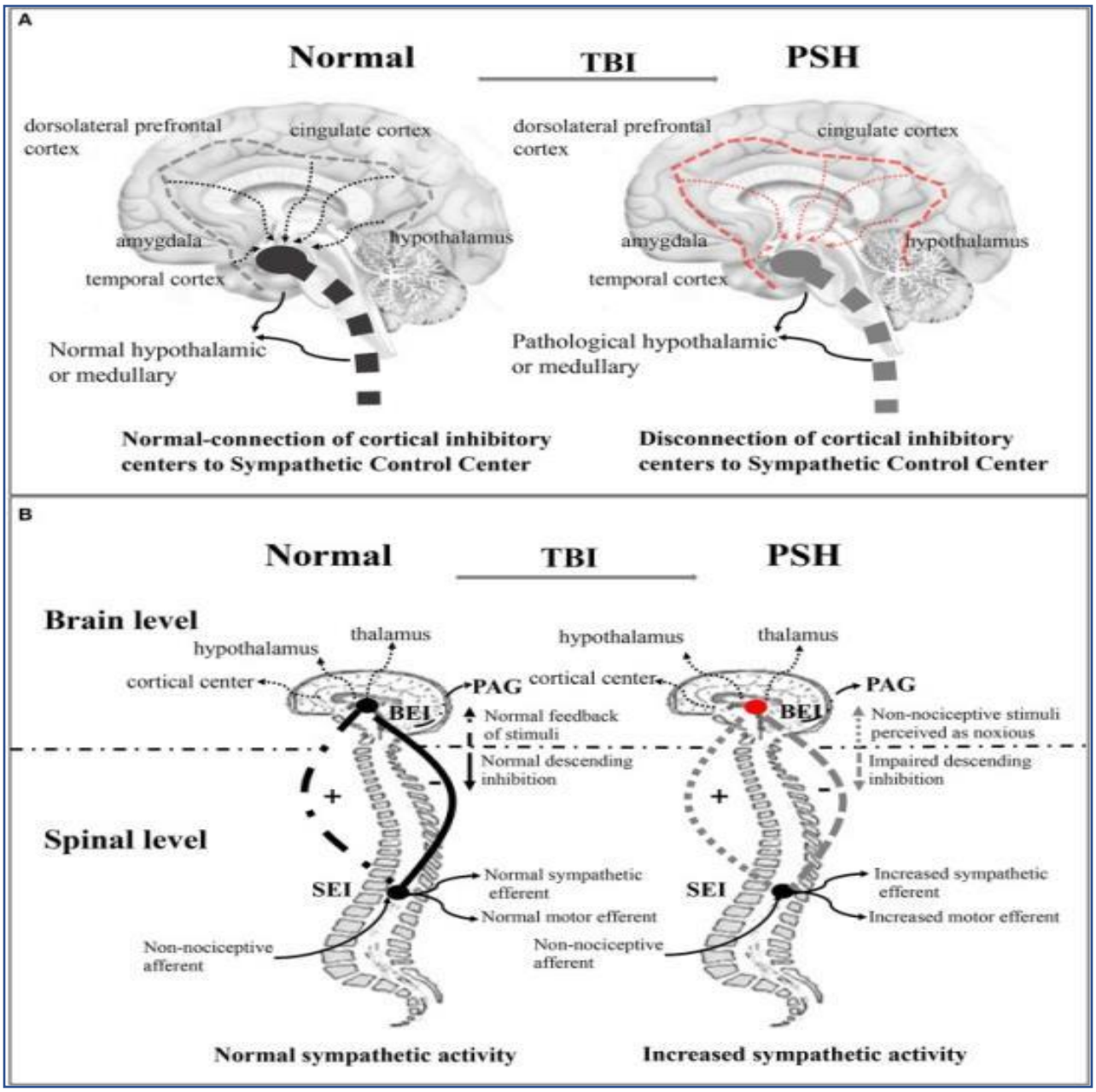

Figure 1: Disconnection theory and excitation-inhibition ratio (EIR) model of the pathogenesis of PSH of the pathogenesis of PSH **[3]**.

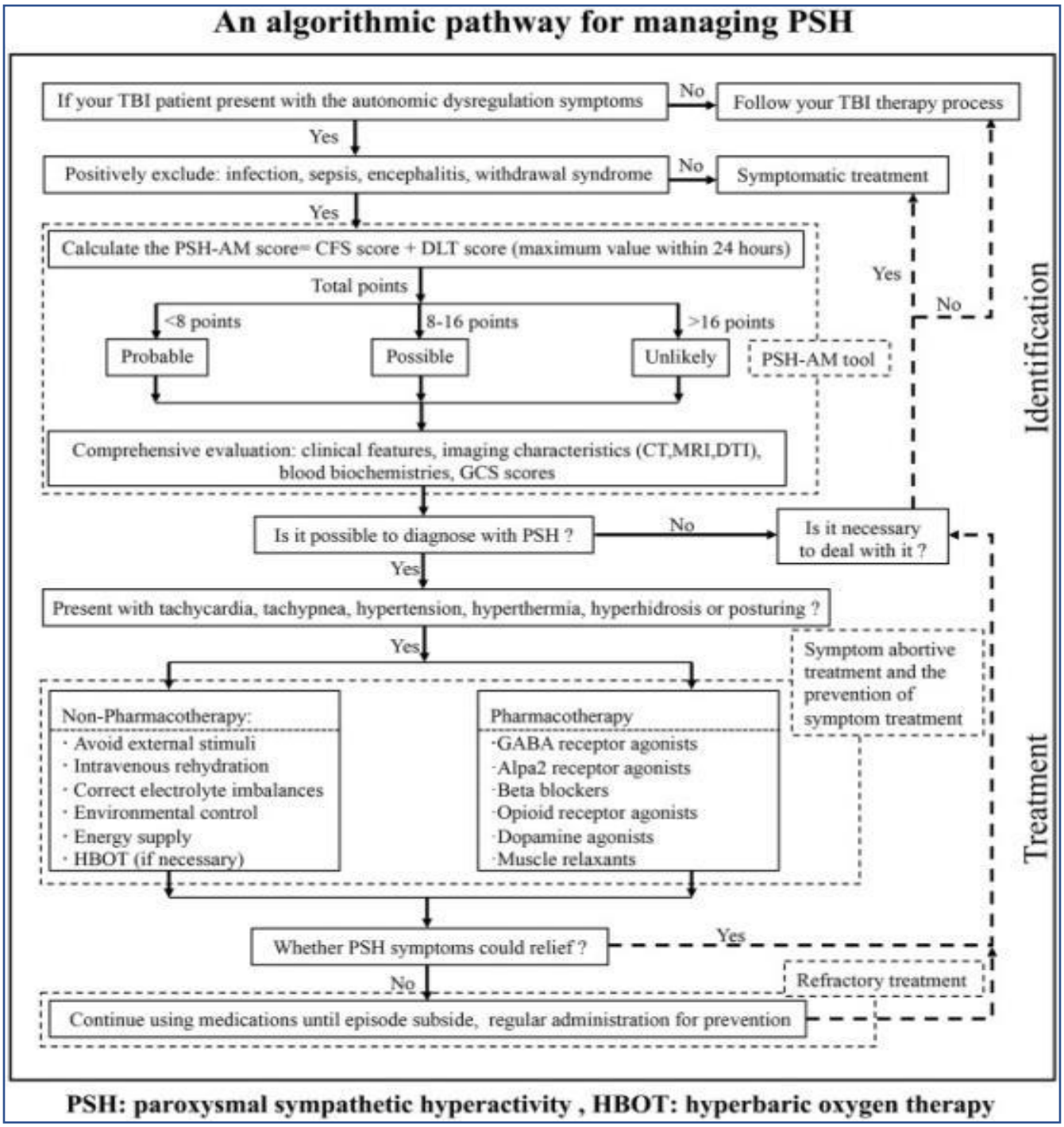

Figure 2: An algorithm for the management of PSH in TBI patients [3]

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