A Review of Paroxysmal Sympathetic Hyperactivity after Acquired Brain Injury

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Severe excessive autonomic overactivity occurs in a subgroup of people surviving acquired brain injury, the majority of whom show paroxysmal sympathetic and motor overactivity. Delayed recognition of paroxysmal sympathetic hyperactivity (PSH) after brain injury may increase morbidity and long-term disability. Despite its significant clinical impact, the scientific literature on this syndrome is confusing; there is no consensus on nomenclature, etiological information for diagnoses preceding the condition is poorly understood, and the evidence base underpinning our knowledge of the pathophysiology and management strategies is largely anecdotal. This systematic literature review identified 2 separate categories of paroxysmal autonomic overactivity, 1 characterized by relatively pure sympathetic overactivity and another group of disorders with mixed parasympathetic/sympathetic features. The PSH group comprised 349 reported cases, with 79.4% resulting from traumatic brain injury (TBI), 9.7% from hypoxia, and 5.4% from cerebrovascular accident. Although TBI is the dominant causative etiology, there was some suggestion that the true incidence of the condition is highest following cerebral hypoxia. In total, 31 different terms were identified for the condition. Although the most common term in the literature was *dysautonomia*, the consistency of sympathetic clinical features suggests that a more specific term should be used. The findings of this review suggest that PSH be adopted as a more clinically relevant and appropriate term. The review highlights major problems regarding conceptual definitions, diagnostic criteria, and nomenclature. Consensus on these issues is recommended as an essential basis for further research in the area.

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Elevated sympathetic nervous system activity occurs in response to trauma, characterized by increased heart rate (HR), respiratory rate (RR), and blood pressure (BP), redeployment of blood to skeletal muscle and the central nervous system, diaphoresis, and hyperthermia. In normal circumstances, the sympathetic response to trauma is proportional to and aimed at reversing the adverse effects of the insult.[1] In the case of traumatic brain injury (TBI), elevated sympathetic activity may almost be considered normal[2,3]; however, as with any homeostatic process, this response has the potential to shift from protective to destructive.[4] Such an excessive response occurs following a variety of acute cerebral insults, where it has been characterized by paroxysmal autonomic and motor overactivity. The resultant condition has been given a wide range of labels, with the nonspecific term of *dysautonomia*[5] being the dominant term in published literature to date. For reasons to be outlined more fully later in this paper, *paroxysmal sympathetic hyperactivity* (PSH)[6] appears to be a more clinically relevant term and will be utilized throughout the remainder of this paper to describe the condition until now referred to as dysautonomia.

This review identified considerable overlap and confusion regarding nomenclature, involvement of different branches of the autonomic nervous system, and the direction of change (ie, hyperactivity vs hypoactivity) in clinical cases in the literature.

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Clinical Relevance

Post-traumatic PSH is an important clinical problem. In a retrospective case-controlled study of subjects with and without PSH,[7] clinical outcomes measured by Glasgow Outcome Scale (GOS),[8] Functional Independence Measure,[9] duration of post-traumatic amnesia,[10] and hospital length of stay (LOS) were significantly worse for the 35 PSH subjects than for the 35 controls. Two subsequent studies confirmed the poorer outcome for PSH subjects as measured by GOS,[3] longer intensive care LOS, and being significantly more likely to require tracheostomy.[11] The longer LOS (in the intensive care unit [ICU] and in hospital overall), the greater need for interventions, and poor clinical outcomes suggest that patients with PSH represented a significant additional burden on healthcare systems.[3]

The clinical relevance of the condition extends beyond simple associations with increased health economic impact and outcome. Excessive sympathetic nervous system activation represents a potentially treatable cause of increased secondary morbidity.[7,12,13] Extreme hypermetabolism during sympathetic storms has been reported,[14] leading to body weight decrease estimated at 25% in the acute period alone.[3] These subjects also have an increased likelihood of developing heterotopic ossification[15]; and hyperthermia after acute brain injury has been found to predict poor outcome,[16–20] probably as a direct cause of secondary brain damage.[21,22] Finally, the prolonged hypersympathetic tone associated with PSH can produce or exacerbate cardiac damage[23] and immune suppression[24] among other problems. It has been postulated that PSH is associated with elevated intracranial pressure; the directionality of this relationship has yet to be determined.[25,26]

In recent years, articles regarding acquired hypersympathetic disorders have been published at an increasing rate, with recent contributions from the disciplines of neurosurgery, intensive care, neurology, and rehabilitation medicine. However, there is currently little agreement on either the diagnostic features or the nomenclature for the condition.[6,7,11,27–29]

Against this background, the current review sought to provide as comprehensive a synthesis of published case literature as possible, while examining and critiquing the reported clinical features, etiologies, and management of the condition. The systematic search strategy used to identify literature is outlined below.

Search Strategy and Selection Criteria

References for this review were identified through searches of online databases (Cumulative Index to Nursing and Allied Health Literature, PubMed, and Medline), 1948 to November 2008, by use of the keywords storm*, autonomic, parox*, dysaut*, variab*, episod*, brain injur*, diencephalic seizure*, diencephalic epilep*, and paroxysmal sympathetic storm*, and Medical Subject Headings (MeSH) autonomic nervous system and brain injuries. Peer- and non–peer-reviewed journal articles, conference proceedings, and book chapters were included. Reference lists of identified articles were hand searched to find previously unidentified articles. Publications known to the authors not otherwise identified by the above search procedure were also included. Clinical studies, case reports, and review articles meeting the following inclusion criteria were identified: (1) human study, (2) diagnosis of brain injury, (3) reporting paroxysmal autonomic overactivity, and (4) published in English.

Clinical and Conceptual Definitions

A description of the literature review process is detailed in the Supplementary Figure. Clinical features associated with acute onset paroxysmal autonomic overactivity in the published case literature revealed a division into 2 distinct categories. This distinction has not been recognized previously, and suggests a need to reconsider the conceptual definition and previous attempts at classifying acquired clinical autonomic hyperactivity.

The first published case of PSH is most commonly ascribed to Wilder Penfield's 1929 case report of JH, a 41-year-old woman with a third ventricle cholesteotoma.[30] This patient displayed paroxysmal increases of BP (110–190mmHg during episodes), with a maximum HR of 100 beats/minute and diaphoresis. The patient displayed Cheyne-Stokes respiration following paroxysms (down to 4 breaths/min), although at other times was tachypneic to 30 breaths/min. Body temperature was below normal during paroxysms. Other features included both pupillary dilatation and contraction, hiccups, and lacrimation. Penfield labeled the syndrome *diencephalic autonomic epilepsy* and reported that the range of features suggested autonomic overactivity of both sympathetic and parasympathetic nervous systems.[30]

In contrast to the above case, contemporary literature typically describes the autonomic hyperactivity as consistent with the sympathetic division alone. Indeed, many authors have specified sympathetic overactivity as the defining characteristic of the syndrome when proposing a term for the condition.[6,31,32] As such, 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 the condition as involving sympathetic hyperactivity alone as it appears in the literature in recent decades.

On this basis, cases were separated into 2 categories (Table 1): those consisting of paroxysmal sympathetic hyperactivity (ie, in the absence of parasympathetic features) and those involving combinations of sympathetic and parasympathetic overactivity (termed mixed autonomic hyperactivity disorders in this review).

Far from an issue of historical semantics, the dichotomy of definitions based on either mixed autonomic or sympathetic hyperactivity appears to have contributed to the confusion evident in current literature. To this juncture, researchers of PSH[26,33–39] and of mixed autonomic hyperactivity disorders[40–42] have both cited Penfield's 1929 case as seminal. Conceptualization of PSH as a spectrum of paroxysmal sympathetic hyperactivity (ie, distinct from mixed autonomic hyperactivity disorders), renders Penfield's 1929 case diagnostically incompatible with PSH.

Instead, the earliest and clearest case report of PSH con-

TABLE 1: Features of Paroxysmal Sympathetic Hyperactivity and Mixed Autonomic Hyperactivity

Category	Clinical Features	Paroxysmal Sympathetic Hyperactivity	Mixed Autonomic Hyperactivity
Sympathetic	Increases in HR, RR, BP, temperature, sweating, and pupillary dilation	Yes	Yes
Parasympathetic	Decreases in HR, RR, BP, temperature, and pupillary contraction	No	Yes
Motor features	Decerebrate posturing, decorticate posturing, spasticity, hypertonia and/or dystonia, teeth-grinding, agitation	Yes	Variable
Other	Hiccups, lacrimation, sighing, yawning	No	Yes

HR = heart rate; RR = respiratory rate; BP = blood pressure; Yes = clinical features present in syndrome; No = clinical features not present; Variable = variable presentation of features.

sistent with the revised definition appears to have been published 25 years later.[43] Penfield presented the case of RS, a 19-year-old man following a severe TBI whose condition satisfies contemporary descriptions of PSH (see Table 1). Clinical manifestations included paroxysmal HR of 180 beats/min, RR of 40 breaths/min, BP of 156mmHg, neurogenic hyperthermia, and decerebrate posturing. Paroxysms were precipitated by afferent stimulation, a feature that has recently been confirmed in empirical research into PSH.[44]

Diagnostic Criteria for PSH

A more recent development is the utilization of diagnostic criteria for PSH. The first diagnostic criteria were published in 1993.[5] Since that time, 8 sets of diagnostic criteria for PSH have been published.[6,7,11,15,28,29,45,98] These criteria differ on a number of points, including time of assessment relative to injury, minimum number of clinical features, and degree of excess for each physiological feature. The differences between criteria have been determined anecdotally, and their potential advantages and disadvantages have not been empirically tested. In the interests of clarity and brevity, this paper focuses on the conceptual definition of PSH rather than addressing the finer points of diagnostic criteria. It is recognized that a consensus-driven, standardized set of diagnostic criteria is an important future development in this field of research.

Focused Summary of PSH Cases

Using the conceptual definition criteria (Table 1), 23 of the 104 papers were considered to report mixed autonomic hyperactivity disorders. Due to the limited number of cases in this group, the wide variation in the clinical features, and the primary focus of this review being on sympathetic hyperactivity, no analysis of the mixed autonomic group was undertaken. This represents an area for future research. Of the 81 publications discussing PSH, 60 reported PSH case data and were included in this review (Supplementary Fig).

These 60 publications yielded 349 cases of PSH. More than half of the PSH cases derive from 4 cohort studies ($n \geq 30$): Dolce et al[29] (retrospective study, n = 87), Fearnside et al[5] (prospective consecutive study, n = 42), Baguley et al[7] (retrospective case-controlled study, n = 35), and Krach et al[45] (retrospective study, n = 31). The remaining cases derive from 10 smaller group studies ($n \geq 5$) and 42 single case or small case series.

Attempting to identify all published cases of PSH in the literature was complicated by confusing and redundant nomenclature, an issue that continues to inhibit progress within the field.[46,47] Almost half the publications in this review were not identified via searchable online databases, and were located via reference lists or articles known to the authors. This highlights the current inadequacy of the syndrome's MeSH tracking in online databases. As a result, it is highly likely that unidentified cases of PSH remain in the literature. This factor and the extensive use of alternate names for the condition appear to have led to the publication of inaccuracies. For example, Oh et al[48] incorrectly cite their paper as the first to report PSH resulting from neoplasia, whereas other cases were reported as early as 1988 under different diagnostic terms.[34,49] Goh et al[31] stated that hydrocephalus or brainstem/diencephalic lesions were found in "all previous cases" of PSH; however, other literature reviews have found this not to be the case.[4,26] These examples support the contention that a definitive, standardized nomenclature would be of great advantage for future research.[13,46,50]

Nomenclature

Thirty-one synonyms for PSH were identified (Supplementary Table 1), indicating marked variability in researchers' use of terminology. One research group introduced 3 new terms for the condition over a 2-year period,[33,34,51] and other authors have utilized multiple terms within a single paper.[11,37,52,53] Since the issue of redundant nomenclature was raised,[7] at least 13 new terms have been published. Few terms have received widespread use after their initial introduction. Only 8 terms have been utilized more than twice after their initial introduction.

TABLE 2: Conditions Preceding Paroxysmal Sympathetic Hyperactivity Onset

Etiology	No.	%	Cases Contributing to Subtotal
Traumatic brain injury	277	79.4	$n < 5$[28,32-35,38,43,49,63,69,74,75,77,86,88-97]; $n < 10$[3,13,15,68,87]; $n < 20$[6,11,98]; $n = 20$[45]; $n = 35$[7]; $n = 42$[5]; $n = 68$[29]
Hypoxia	34	9.7	$n < 5$[6,14,28,46,71,73,81-83,89,92]; $n < 10$[29,45]
Stroke	19	5.4	$n < 5$[6,34-36,72,88,92,99]; $n = 8$[29]
Hydrocephalus	9	2.6	$n < 5$[34,37,51,78,79,100]
Tumor	2	0.6	$n < 5$[31,49]
Hypoglycemia	1	0.3	$n = 1$[70]
Infectious	1	0.3	$n = 1$[29]
Unspecified	6	1.8	$n < 5$[28,45,101]
Total	349	100	

Unspecified = original article did not state etiology; No. = total number of reviewed cases; n = number of cases in individual studies.

To assist the process of establishing a single term for the condition, the nomenclature can be grouped into a number of subsets: terms suggesting an epileptogenic cause, terms inferring structural pathology, and the larger group that utilizes clinically descriptive terms. Viewed in this way, there are good reasons to exclude terms in the first 2 groups. To date, there are no empirical data suggesting an epileptogenic etiology for PSH (see the Pathophysiology section). Furthermore, the pathophysiology of PSH is poorly understood, and as such it seems presumptive to use a term invoking hypothetical anatomical areas of involvement. The clinically descriptive group includes *dysautonomia*, the term until now used by authors of this paper and the most dominant term in the scientific literature. This term is less than satisfactory as it is a generic umbrella term that includes all syndromes with autonomic abnormalities, and does not identify whether the syndrome's features are parasympathetic or sympathetic, hyperactive or hypoactive.

The common clinical features in the cases reviewed point to the paroxysmal, sympathetic nature of the overactivity. The data regarding motor manifestations are less defined, involving decerebrate or decorticate posturing, dystonia, rigidity, and spasticity. Taken together, the combined clinical features reduce the applicability of terms such as *paroxysmal autonomic instability with dystonia*. For these reasons the authors propose that the most clinically accurate and descriptive term for the condition is *paroxysmal sympathetic hyperactivity*, a term introduced by Rabinstein in 2007.[6]

Etiology

This review identified several types of acquired brain injury (ABI) preceding PSH onset (Table 2). PSH was most commonly associated with TBI, accounting for 277 of the 349 reported cases. The higher prevalence of post-TBI PSH compared to non-TBI (ratio of 4:1) supports the findings of 2 group studies, in which the ratio of PSH post-TBI to non-TBI was 5.5:1 in ICU[6] and 2:1 for subjects in a vegetative state.[29]

Hypoxic brain injury was the primary etiology in 9.7% of PSH cases. Whereas the proportion of cases associated with hypoxia was substantially lower than TBI, 1 study found a much higher incidence of PSH following hypoxia (29%, 9/31 cases) compared to TBI (14%, 20/146 cases).[45] Another study identified significant preadmission hypoxia in 22/35 subjects with PSH following severe TBI.[7] It therefore seems likely that severe hypoxic brain injury is a significant pathophysiological contributor to PSH; however, the greater community incidence of TBI gives a much higher overall prevalence of PSH arising from this disorder. PSH following stroke formed the third largest etiological subgroup (5.4%, 19 cases), with hemorrhagic stroke more commonly associated with PSH than ischemic stroke (ratio of 4:1). How (and whether) the neurogenic hyperthermia and hypersympathetic drive of aneurysmal subarachnoid hemorrhage differ from PSH has not been investigated to date.[54,55] Other non-TBI related cases of PSH were rarely reported.

In contrast, mixed autonomic hyperactivity disorders predominately occurred in either congenital or nontraumatic cases of brain impairment, including patients with agenesis of the corpus callosum[32,35,37,56,57] and tumors.[30,41,42,58–60] Only 1 mixed autonomic hyperactivity case was reported following TBI.[61] The divergence in etiology between PSH and the mixed autonomic hyperactivity disorders supports the differentiation of these cases into different groups. However, it should be noted that publication bias may be a contributing factor to this apparent etiological differentiation.

There are a number of conditions with a similar clinical appearance to PSH. These overlap syndromes include autonomic dysreflexia, malignant hyperthermia, and Irukandji syndrome.[62] With a few exceptions, there is an association with a clear precipitating event (eg, a jellyfish sting, high thoracic spinal

TABLE 3: Sample Characteristics of Paroxysmal Sympathetic Hyperactivity Cases

Characteristic	Value
Age, mean yr ± SD	24.2 ± 11.8
Sex, No. (%)	
Male	112 (78)
Female	31 (22)
GCS severe injury [<9], No. (%)	199 (100)
GOS, No. (%)	
1: Death	22 (18)
2: PVS	37 (30)
3: Severe disability	56 (45)
4: Moderate disability	7 (5)
5: Good recovery	3 (2)
Clinical setting, No. (%)	
ICU	139 (45)
Rehabilitation	119 (39)
Combined	48 (16)

Available data varied (total, n = 349; age, n = 279; sex, n = 143; GCS, n = 199; GOS, n = 125; clinical setting, n = 306). SD = standard deviation; GCS = Glasgow Coma Scale[66] at emergency department admission; GOS = Glasgow Outcome Scale[8]; PVS = persistent vegetative state; ICU = intensive care unit.

cord injury, recent anesthesia) to assist in distinguishing non-PSH causes of sympathetic overactivity. In the acute ABI setting, however, the onset of PSH may be difficult to differentiate from sedation withdrawal, sepsis, or systemic inflammatory response syndrome. However, these conditions usually resolve in a shorter timeframe than PSH, and the latter case is associated with hypotension rather than hypertension. Confusion between PSH and autonomic dysreflexia following high spinal cord injury is unlikely, as the conditions present quite differently in their acute presentation (see Baguley[4] for review). Similarly, diagnoses such as pheochromocytoma (which can be unmasked by trauma[63]), carotid sinus injury, and acute baroreceptor failure[64] were not identified in the reviewed cases.

Natural History

In cases identified by this review, patients with PSH were typically young males who had sustained a severe TBI (Table 3). The higher prevalence of TBI in the sample (4:1 against all other etiologies) resulted in a mean age and male:female ratio of PSH cases consistent with the general patterns of TBI hospital admissions.[65]

The estimated incidence of PSH resulting from TBI ranges from 7.7% to 33% of TBI ICU admissions.[3,5,6,11,15,29,45] It appears the higher end of this range refers to a transitory, short duration variant, estimated to occur in between 24%[3] and 33%[6] of patients with moderate or severe TBI during the acute stage of recovery. These figures contrast with the prolonged variant of PSH (lasting weeks to months), the incidence of which is estimated to range from 7.7% to 14.1% following severe TBI.[3,11,15,45] The highest incidence of prolonged PSH was recently reported by Dolce et al,[29] with $\frac{1}{3}$ of their severe TBI sample experiencing PSH.

Overall, cases reported in the literature were evenly split between those identified in an ICU versus identification in a rehabilitation setting. Few of the papers (16% of all cases) collected longitudinal data across these 2 clinical settings. Where reported, all subjects sustained a severe brain injury (acute admission Glasgow Coma Scale < 9),[66] generally leading to poor outcome (GOS ≤ 3). Although only a small proportion of PSH cases (7%) achieved a moderate or good recovery (GOS ≥ 4), it is important to underline that these outcomes derive from a context where treatment has been inadequately researched and implemented.[50,67,68]

It has been proposed that the substantial interstudy differences in clinical presentation are a function of time postinjury, with higher incidence of PSH identified immediately postinjury[3,6] and lower incidence figures reported during rehabilitation.[3,11,15,45] Other potential factors include differing diagnostic criteria[6,13,62] and study referral bias.[3,7,29]

Management

Forty-three of the 60 articles referenced the effectiveness of pharmacological management for PSH (Supplementary Table 2). The methodological quality of this evidence was low, precluding detailed analysis of treatment effects. The available evidence is borne out of case reports or small case series, with evaluation of treatment efficacy largely based on anecdotal decrease in sympathetic and motor hyperactivity. In this regard, interpretation of published data is confounded by 2 major methodological limitations. First, there is a historical lack of standardized outcome measures to evaluate treatment efficacy. Very few authors specified the outcome measures used to determine efficacy, and others listed medications without describing their effect on clinical features of PSH at all. Two studies used qualitative assessment to describe the effect of intervention on clinical parameters such as fewer paroxysms or paroxysms of reduced intensity.[68,69] Attempts to quantitate treatment effects were reported in a small number of studies[7,35,49,70]; however these studies lack adequate methodological rigor by current evidence-based standards.

The second major limitation is the small number of reported cases. For many medications, the available evidence is limited to a single case report. For example, case reports of ineffective medication trials have included trihexyphenidyl,[71] diphenhydramine,[71] propranthe line,[72] hydroxyzine,[71] and hydralazine.[14] Beneficial medication case reports include sodium amytal,[43] thorazine,[36] botulinum toxin A,[73] codeine,[35] dexmedetomidine,[74] prazosin,[72] and oxycodone.[75]

In terms of subject numbers and trial design, the strongest evidence currently available supports the use of intrathecal ba-

clofen (Supplementary Table 2). However, this intervention is invasive, costly, not always available, and has an appreciable complication rate of 20 to 50%.[76] It has therefore been proposed that oral medication trials be attempted in the first instance[4,50,67]; however, orally administered baclofen has generally been reported as ineffective.

The cumulative, albeit limited, evidence from this review suggests that first line oral medications could include most opioids, gabapentin, benzodiazepines, centrally acting α-agonists, and β-antagonists (Supplementary Table 2). Bromocriptine could be considered a second line medication often used in combination with other medications, for example, bromocriptine and morphine. The poor methodological quality of studies available to date prevents stronger evidence-driven recommendations regarding current best practice for management of PSH.

In addition to pharmacological intervention, this review identified a small number of publications describing other treatment approaches, including surveying for untreated pain conditions.[67,77] The increased risk of developing heterotopic ossification in PSH patients[15] suggests that PSH patients require routine investigation and management, thereby reducing a potential nociceptive stimulus—a known trigger of sympathetic paroxysms. A small number of studies describe interventions such as shunt revision,[78] splinting to improve limb positioning, periods of rest, and avoidance or pretreatment of known nociceptive triggers such as bathing, turning, and endotracheal tube suctioning[77]; however, limited quantitative data are available to support the effectiveness of these intervention approaches. There also appears to be a role for nutrition replacement therapy relating to the caloric energy and replacing the insensible fluid losses associated with higher metabolic rate and diaphoresis.[7]

Pathophysiology

The pathophysiology of PSH has not been extensively investigated and, until very recently, theories of pathophysiology had not been empirically tested. In the earliest reports of PSH identified by this review, the condition was thought to be epileptogenic in nature, hence the inclusion of *epilepsy* or *seizure* in the early terms used for the syndrome (Supplementary Table 1).[39,43,79,80] However, studies that subsequently attempted to identify seizure activity in PSH utilizing electroencephalography produced negative findings,[31–33,36,38,49,69,74,77,81–83] and most anticonvulsants are reported to be ineffective in controlling the condition (Supplementary Table 2). As a consequence of these observations, most authors have invoked some form of disconnection theory.[26] These theories mostly assume that brainstem excitatory centers are released from higher control with a resultant hypersympathetic state. Alternatively, another disconnection theory, the Excitatory/Inhibitory Ratio model, posits that the causative brainstem centers are inhibitory in nature, and that sympathetic hyperactivity originates at the spinal cord level in a process analogous to autonomic dysreflexia following high thoracic spinal cord injury.[62]

Publications that reported elevated catecholamine levels after ABI did not detail sufficient clinical information to determine whether subjects would be included in the PSH group.[84,85]

A number of clinical studies have identified an association between afferent stimuli and sympathetic paroxysms. Reactivity to stimuli was reported in the first published case of PSH,[43] an observation corroborated by numerous anecdotal case reports for both noxious and non-noxious stimuli such as bathing, turning, and tracheostomy care.[7,32,36,38,52,63,67,69,77,79,81,82,86] These observations have been quantitated in recent empirical studies involving endotracheal tube suctioning[52] and botulinum toxin A injections.[44] The cumulative evidence from earlier descriptive and more recent quantitative studies supports the contention that over-reactivity to afferent stimuli may be the hallmark of PSH.[52] However, the limited empirical evidence suggests that much work remains to be done to elucidate the pathophysiology of PSH.

Numerous researchers have proposed lesion locations associated with PSH, and these have been reviewed elsewhere.[26] One study found associations between PSH and brainstem injury, and diffuse axonal injury.[7] Given the disparate reports and postulations of lesion location and theories, the authors of this paper have avoided further speculation.

Future Directions

Despite the methodological limitations of early publications, recent literature in PSH after ABI has shifted from case reports to prospective empirical research. The introduction of objective, quantitative measures to investigate the condition will strengthen future research design, enabling evaluation of treatment efficacy.[13,70,87] With the advent of robust measures to objectively define the sympathetic overactivity seen in PSH, future efforts should be targeted at multicenter, large sample studies to objectively evaluate the incidence and natural history of the syndrome.[12,44,77]

The limited data suggest that there are no clinical differences in presentation between hypoxic and TBI etiologies of PSH, indicating that although post-TBI PSH provides the best defined and most accessible model for research,[13,52] grouping PSH data from multiple etiologies (eg, TBI, hypoxia, stroke) may be an acceptable approach. Due to the relative rarity of the condition, such a process would allow sufficient numbers of subjects to produce an evidence-based set of diagnostic criteria, quantify treatment efficacy, and confirm the pathophysiological mechanisms underlying the condition.

Finally, we suggest that the nonspecific term *dysautonomia* no longer be used to describe the syndrome, and that PSH is a more specific and clinically relevant term. However, it is recommended that a working party of interested researchers be established to formalize moves toward a consensus position for nomenclature. Furthermore, a consensus approach to developing formal diagnostic criteria for the condition should be pursued. These steps would represent a maturation of research into the syndrome characterized by PSH, and maximize the consistency and quality of future research. Recommendations for future research are summarized as:

- Establishment of an expert group for consensus on:
  - Nomenclature.
  - Diagnostic criteria.
  - Management guidelines.
- Development of robust tools to diagnose and measure treatment efficacy.
- Multicenter research to produce data-driven diagnostic criteria and management guidelines.

Limitations

The original intent of this review was to systematically critique existing clinical studies for quality and consistency. However, it became clear that such an approach is not appropriate at this time. As discussed, confusing nomenclature, inadequate literature search terms, and variable diagnostic criteria present limitations at the present time. Despite these limitations, the current review adds a significant degree of clarity to the area and provides the most complete collection of literature to date. Another limitation to this review was the low methodological quality of published reports and studies, with the literature base dominated by single case studies and small case series. Diagnostic criteria were often not reported, were anecdotal, or used 1 of 9 sets of overlapping diagnostic criteria[5–7,11,15,28,29,45,98] that have been shown to result in different diagnostic groupings.[27] Publication bias may have affected the reported frequencies of associations with PSH, such as etiology or severity of injury. Further prospective observational studies are required to definitively document the clinical pattern of PSH and assess the efficacy of therapies.

Conclusions

This review provides the single largest collection of published cases of PSH. Based on this literature, it is proposed that this clinically descriptive term be used for the condition pending consensus-based ratification and that it should be differentiated from cases where there is mixed autonomic hyperactivity. Although PSH follows various types of ABI, the literature predominantly relates to traumatic (79%) and hypoxic (10%) brain injury. The current evidence for management and pathophysiology of PSH is very limited, and requires rigorous methodology in future studies. Such research would be greatly facilitated by a consensus on nomenclature, diagnostic criteria, and investigational tools.

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Potential Conflicts of Interest

None of the authors has any conflicts of interest.

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