Paroxysmal Sympathetic Hyperactivity: the storm after acute brain injury.

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Summary:

A substantial minority of patients surviving acquired brain injury develop a state of sympathetic hyperactivity that may persist for weeks or months, consisting of periodic episodes of increased heart rate and blood pressure, sweating, hyperthermia, and motor posturing, often in response to external stimuli. The unifying term for the syndrome, Paroxysmal Sympathetic Hyperactivity (PSH), and clear diagnostic criteria defined by expert consensus, were only recently established. PSH has predominantly been described after traumatic brain injury, where it is associated with worse outcome. The pathophysiology is incompletely understood, although most researchers consider it a disconnection phenomenon with paroxysms driven by a loss of inhibitory control over excitatory autonomic centers. While therapeutic strategies to mitigate the sympathetic outbursts have been proposed, their effects on PSH are incomplete, inconsistent, and unpredictable; and influence on outcome unknown. Drug combinations are frequently used, and chosen based on local custom, rather than objective evidence. New rigorous tools may allow a better characterization of patients with PSH for future trials of therapy.

Introduction

Excessive sympathetic nervous system activity can develop after severe acquired brain injury, with about 80% of cases occurring after traumatic brain injury (TBI). This condition can present dramatically,[1] with paroxysmal tachycardia, arterial hypertension, tachypnea, hyperthermia, and decerebrate posturing, precipitated by afferent stimulation. It was first described in TBI by Wilder Penfield [2], and the assumption of an epileptic etiology gave the syndrome its first name, 'mesencephalic seizures'. In over 350 subsequently published cases up to 2010[3] in the critical care and rehabilitation literature, the same syndrome had over 31 different labels, some more descriptive (e.g. 'dysautonomia', 'autonomic storms', or 'sympathetic storms'), some referring to an assumed (epileptic) mechanism (e.g. 'autonomic seizures'), or to the site of damage (e.g. 'hypothalamic storms'). [3–6] This lack of a clear terminology and definition were probably both cause and consequence of the under-recognition of this syndrome, despite its relatively high incidence after severe brain damage [7,8], the significant association with morbidity [9–12], and its high health care and societal costs [7]. It might also explain the slow progress in understanding its pathophysiology, further compounded by a failure to distinguish between mixed parasympathetic/sympathetic,[13] and pure sympathetic hyperactivity, with conflation of both in a single diagnosis for many decades.[3] Although conclusive evidence of the absence of parasympathetic involvement is unavailable, the current consensus is that autonomic hyperactivity in this syndrome only concerns the sympathetic division.[3,12,14]

In 2010 the term 'paroxysmal sympathetic hyperactivity' (PSH), introduced in 2007 by Alejandro Rabinstein [12], was adopted as the single unifying term for this condition [3]. Four years later, in 2014, 60 years after the first published case, an expert group [15] established a rigorous conceptual definition and diagnostic criteria. These criteria should provide a foundation for more systematic research on this clinical syndrome and its management.

Several different classes of agents, acting at a range of molecular targets have been used in PSH, with varying success in each case. The syndrome of PSH is likely to be mechanistically heterogeneous, and identifying the dominant pathophysiology that is responsible for the clinical picture in any given patient could allow more rational matching of patients to therapies, and move towards precision medicine in PSH. The recent development of clear diagnostic criteria for the condition has provided the essential first step in such an exercise, since it clearly defines the initial population of patients who might be the subject of such therapeutic stratification.

The purpose of this Series paper is to provide an overview of the existing literature on PSH, its causes, consequences, pathophysiology, and diagnosis; and to discuss the current evidence on therapeutic options. Although the dominant underlying aetiology in PSH is TBI, insights obtained from patients with other aetiologies of disease who satisfy the criteria for PSH show substantial commonalities in pathophysiology and therapy response, and therefore PSH of all causes is covered here.

Definition and diagnostic criteria

Between 1993 and 2008, 9 sets of diagnostic criteria for this syndrome were published,[9,10,12,16–21] which differed with regards to timing of occurrence or assessments relative to the injury, the number of clinical features required, and the degree of deviation from normal of clinical parameters (heart rate, blood pressure, temperature, etc.).[22] An international consensus process in 2014[15] addressed confusion regarding nomenclature, produced diagnostic criteria, developed a diagnostic tool, and reached agreement on the adoption of the term 'Paroxysmal Sympathetic Hyperactivity (PSH)' as a label for this condition, which was further defined as:

> *"A syndrome, recognized in a subgroup of survivors of severe acquired brain injury, of simultaneous, paroxysmal transient increases in sympathetic (elevated heart rate, blood pressure, respiratory rate, temperature, sweating) and motor (posturing) activity."*

The Expert Group selected 11 of 16 previously reviewed features[22] as pathognomonic of PSH (Supplementary Table 1), and proposed a clinical scoring system - the PSH assessment measure (PSH-AM) (Table 1) - as an aid to diagnostic consistency. The PSH-AM consisted of two separate constructs: first, the clinical feature scale (CFS), to score the presence and severity of excess adrenergic and motor activity; and second, the diagnosis likelihood tool (DLT), to score the likelihood of the presence of PSH. A paediatric adaptation of the CFS has also been proposed (Supplementary Table 2).[23] While useful, a definition by consensus still has limitations, and a clear link with pathophysiology, the independent contribution of PSH to clinical outcomes, and a more precise definition of the duration of a paroxysm, are currently lacking.

A.

Clinical Feature Scale score:	0	1	2	3
Heart rate (per min)	<100	100–119	120–139	≥140
Respiratory rate (per min)	<18	18–23	24–29	≥30
Systolic blood pressure (mmHg)	<140	140–159	160–179	≥180
Temperature (^{0}C)	<37·0	37·0–37·9	38·0–38·9	≥39·0
Sweating	Absent	Mild	Moderate	Severe
Posturing during episodes	Absent	Mild	Moderate	Severe

B.

Diagnosis Likelihood Tool: one point per feature present
Antecedent acquired brain injury
Clinical features occur simultaneously
Episodes are paroxysmal in nature
Sympathetic over-reactivity to normally non-painful stimuli
Absence of parasympathetic features during episodes
Features persist >3 consecutive days
Features persist ≥2 weeks post-brain injury
≥2 episodes daily
Absence of other presumed causes of features
Features persist despite treatment of alternative differential diagnoses
Medication administered to decrease sympathetic features

C.

Interpretation of scores

- **CSF subtotal**=sum of CSF scores for each of the six features (0–3 points for individual features; maximum subtotal=18); **CSF subtotal severity scores**: 0=nil; 1–6=mild; 7–12=moderate; ≥13=severe
- **DLT subtotal**=sum of points for each feature present (one point per feature; maximum subtotal=11)
- **PSH–AM**=CFS subtotal + DLT subtotal; PSH–AM <8=PSH unlikely; 8–16=PSH possible; ≥17=PSH probable

Figure 2. The Paroxysmal Sympathetic Hyperactivity–Assessment Measure

The Paroxysmal Sympathetic Hyperactivity–Assessment Measure (PSH–AM) is calculated using two constructs—the Clinical Feature Scale (CFS), which measures the intensity of the cardinal features identified as crucial to PSH, and the Diagnosis Likelihood Tool (DLT), based on the presence of contextual attributes (identified by expert consensus), which indicates the likelihood that the observed features are due to PSH. The combined CFS and DLT scores provide the PSH–AM score, which is an estimate of the probability of a diagnosis of PSH. Adapted from Baguley et al,[15] by permission of Mary Ann Liebert, Inc.

PSH has been described at all stages following brain injury - from early critical care through to the rehabilitation phase. Patients are often sedated acutely to minimize secondary brain injury, and classical features of PSH may not be manifest until sedation has been weaned. Despite this, the diagnosis may be made as early as within the first week post-TBI, even while patients remain sedated.[24] While patients may exhibit features of PSH in the absence of provocation, it is far more common for these to be provoked by

non-noxious stimuli, or present as a pathologically prolonged physiological responses to noxious stimuli, which in the absence of PSH might only result in short lived responses in heart rate and blood pressure. The duration of the paroxysmal phase is variable, ranging from less than 2 weeks to many months, after which the syndrome may "burn out", leaving, in many cases, residual dystonia and spasticity.[18] It remains unclear whether the residual spasticity is truly part of the sequelae of PSH, or simply the consequence of injury to supraspinal motor tracts, which happens to coincide with PSH as both are seen more commonly in more severe injury. It is certainly possible for PSH to resolve without residual spasticity.

Epidemiology

A review of all 349 published PSH cases prior to 2010[3] found that about 80 % followed TBI, 10% postanoxic brain injury, 5% stroke, and the remaining 5% occurred in association with hydrocephalus, tumor, hypoglycemia, infections or unspecified causes. This high prevalence of TBI-related cases is not completely explained by the high absolute incidence of TBI, and may be intrinsically higher when compared to other causes of brain injury. One series of consecutive febrile neurocritical care patients reported an incidence of 33% post-TBI, compared to 6% after other causes of brain injury.[12] Regardless of underlying diagnosis, reported incidence rates in other studies, from several countries, range from 8% to 33%.[7,9,12,16,25,26] The rates of PSH may be changing over time. A recent Italian survey of 333 patients in a vegetative state after massive brain injury[21,27] described a decreasing incidence of PSH over time, falling from 32% (for TBI) and 16% (for other aetiologies) between 1998-2005, to 18% and 7% between 2006-2010. Further studies are needed to confirm this trend, and to determine its causes. The literature on PSH in paediatrics is limited, but broadly similar. In a large paediatric case series[4], (n=249), the incidence after TBI was 10%, and 31% after cardiac arrest. More recently, Pozzi[28] performed a retrospective analysis of all 407 children, admitted to their neurorehabilitation unit after discharge from an ICU following acute brain injury, between 2001 and 2011, and was able to identify 26 cases of PSH, of which 12 after TBI, 9 post-anoxic, and 5 due to other causes. One smaller study suggests that PSH is twice as frequent in severe hypoxic injury compared to TBI in children[17]. An even higher incidence of 41% was found in series of 72 children with encephalitis and meningo-encephalitis [29].

This wide range in reported incidence underlines the difficulties in estimating the true incidence of PSH. Factors that explain large between-study differences include: study design (a subset of severe brain injury versus consecutive cases), unit admission criteria, type and severity of brain injury, the choice of diagnostic criteria, competing events such as non-survival, and publication bias. The difference in incidence is influenced by the timing of assessment,[7] with 24% of subjects meeting criteria at day 7 post injury,

decreasing to 8% at two weeks, in one study. Furthermore, the perceived incidence in subacute units is often higher than in ICU, possibly due to 'clustering' effects of patients with more severe injuries being preferentially admitted for rehabilitation. In addition, stopping powerful analgesics, mainly opioids, upon transfer from the ICU to the rehabilitation center, might unmask PSH symptoms.

Impact on outcome

The higher likelihood of PSH after more severe and more diffuse brain injuries with an inherent association with worse hospital or long-term clinical outcomes makes the assessment of the independent contribution of PSH to this outcome a challenge. Before 1999, reports on the outcome of PSH patients were scarce. In a large multicenter study of TBI patients in 1993, autonomic hyperactivity was not an independent risk factor for mortality or poor clinical outcome,[16] but a subsequent study reported longer hospital stay and worse clinical outcome in PSH patients compared to matched controls,[18] corroborated in a subsequent case series from the same centre.[7] In a dedicated institute for patients in a vegetative state, a diagnosis of 'dysautonomia' was associated with a worse Glasgow Outcome Scale (GOS) in both TBI and non-TBI patients in two studies separated by 5 years.[21,27] A similar association with prolonged hospitalization and worse clinical outcome was described in a Chinese study,[26] but other studies reported less consistent impact on hospitalization outcomes, such as duration of mechanical ventilation, or ICU, hospital, or rehabilitation length of stay (LoS); and no effect on long-term neurological outcome [8,9,30,31]. The results of these studies are summarized in Table 2.

Between-study discrepancies may reflect the methodological issues mentioned above, inherent to case series. In addition, common outcome measures (such as GOS or Functional Independence Measure (FIM)) may be too insensitive to assess subtle differences in neurological status at the worse end of the outcome scale. Further, the impact of PSH may reflect a spectrum, with a shorter duration syndrome (which may be driven by sedative and opioid withdrawal) not affecting outcome, while longer persistence of the syndrome being associated with significant negative consequences for recovery. [24] Available data do not allow us to address this hypothesis, or determine whether differences in patient management modulate the relationship between PSH and outcome. Notwithstanding these uncertainties, the overall clinical impression is that PSH is an independent risk for poorer neurological outcome.

Table 1: Outcomes of patients with and without PSH

Study details (1)	Duration of mechanical ventilation (2)	ICU/Hospital Length of Stay (2)	Rehabilitation Length of Stay (2)	Proportion of patients with tracheostomy (3)	Incidence of infections (3)	GOS (4)	FIM (4)
Baguley, TBI (35/70)[18]	NA	Longer/Longer	Longer	NA	=	Worse	Worse
Fernandez-Ortega, TBI (11/37)[9]	Longer	Longer / NA	NA	Higher	Higher	=	NA
Dolce, Vegetative, mixed (333)[21]	NA	Longer/Longer	NA	NA	NA	Worse	NA
Hendricks, TBI[30]	Longer	NA	NA	NA	Higher	=	NA
Lv, TBI (16/87)[26]	=	Longer/Longer	NA	Higher	Higher	Worse	NA
Fernandez-Ortega, TBI (18/179)[8]	Longer	Longer/Longer	NA	Higher	Higher	=	NA
Laxe, TBI (13/39)[31]	NA	NA / Longer	Longer	NA	NA	=	=
Hinson, TBI(16/102)[34]	NA	= / NA	NA	NA	NA	=	NA
Pozzi, mixed pediatric (26/407)[28]	NA	NA	NA	Higher	NA	NA (5)	NA (5)
Mathew, TBI (29/343)[53]	NA	= / Longer	NA	NA	NA	Worse	NA

Table 1 legend:
Symbols: = : no statistical difference; NA : not assessed;
(1) Study details: First author, type of brain injury, (number of patients with PSH/total number of patients studied).
(2) 'Longer' refers to a longer duration of mechanical ventilation or a longer length of stay, of PSH patients in comparison with non-PSH patients.
(3) 'Higher' refers to a higher proportion of patients with tracheostomy or a higher incidence of infections, of PSH patients in comparison with non-PSH patients.
(4) GOS: Glasgow outcome scale; FIM: Functional Independence Measure; 'Worse' refers to worse performance on these outcome scales, of PSH patients in comparison with non-PSH patients.
(5) Although the pediatric case series by Pozzi et al[28] did not report GOS or FIM, there was a higher incidence of permanent vegetative state as well as a higher mortality during follow-up.

Pathophysiology

Initially proposed epileptogenic mechanisms [2,13] for PSH have not found experimental support. Current hypotheses propose that combinations of diffuse and/or focal injury 'disconnect' one or more cerebral centres from caudal excitatory centres. [32,33,34] An initial synthesis of this hypothesis postulated a simple

disconnection of cortical inhibitory centres (such as the insula and cingulate cortex) with hypothalamic, diencephalic and brainstem centres responsible for supraspinal control of sympathetic tone.[32] While this scheme explained aspects of PSH (such as dystonia), it failed to provide a complete explanation of all of its features[32]. A more recent proposal, the Excitatory: Inhibitory Ratio (EIR) model[33,34] proposes a two-stage process with the loss of descending inhibition allowing excitatory spinal circuits to develop (figure 1).

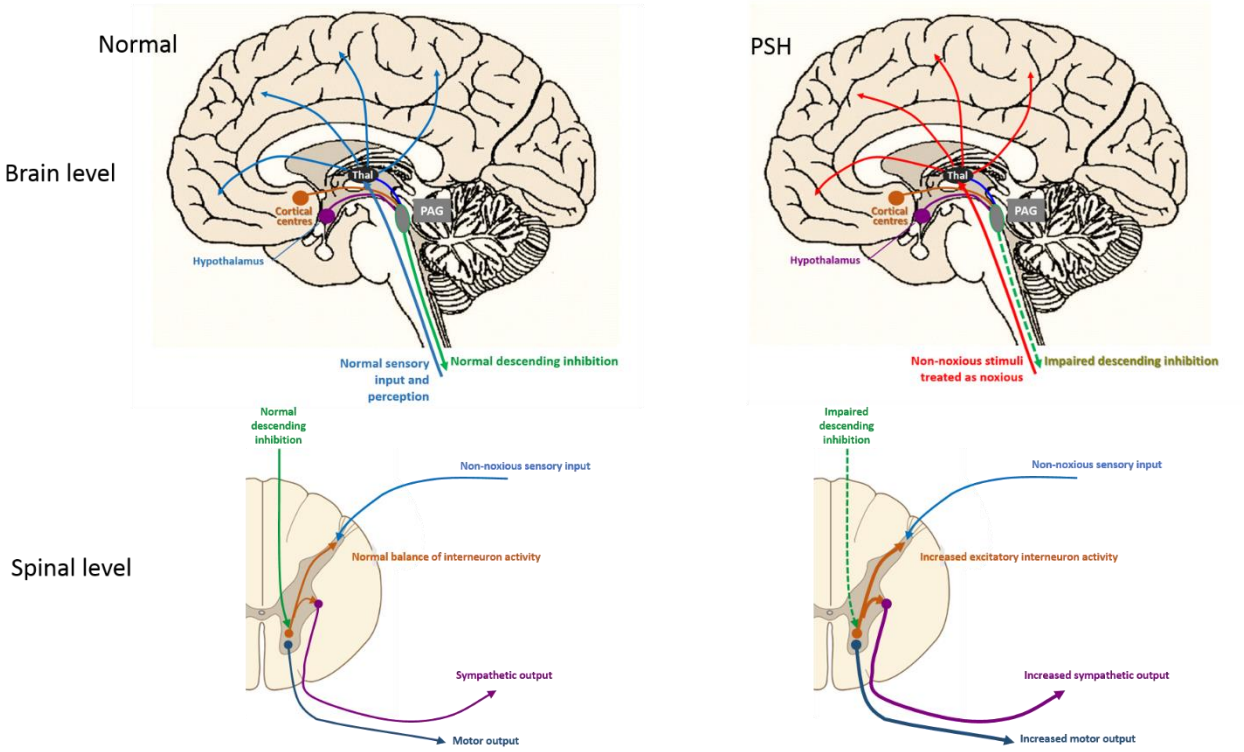

Figure 2. Excitatory-inhibitory ratio model for pathogenesis of PSH.

In normal circumstances, various cortical, hypothalamic, thalamic, and other subcortical inputs modulate activity within brain stem centres (the periaqueductal grey (PAG) is shown here as one of the key brainstem hubs in this process). In turn, these brainstem nuclei provide inhibitory drive to spinal reflex arcs, thereby maintaining balance between inhibitory and excitatory interneuron influences on motor and sympathetic efferents, and allow normal sensory stimuli to be perceived as non-noxious. In the EIR model of PSH, disconnection of descending inhibition produces maladaptive dendritic arborisation and spinal circuit excitation, with non-noxious stimuli triggering increased motor and sympathetic output (spinally) and potentially becoming perceived as noxious (centrally).[33,56]

Paroxysms then settle with recovery of the inhibitory drivers. This model also explains the pathologically increased and prolonged response to stimuli that are either non-nociceptive (movement) or only minimally nociceptive (such as tracheal suction), as an allodynic response, reminiscent of the phenomena seen in

chronic pain syndromes.[55] Non-PSH literature suggests a putative role for the periaqueductal grey matter as a central inhibitory driver,[56] with midbrain lesions implicated in the functional/structural disconnection underlying the more severe end of the severity spectrum. It also explains some outcome differences, as patients with more rapid recovery of supraspinal inhibition are likely to have shorter duration PSH and have less brainstem involvement overall.

Several attempts have been made to determine the location of structural lesions that increase the likelihood of developing PSH, but the data from clinical imaging are equivocal. In TBI, PSH has been variably associated with diffuse axonal injury (DAI) and younger age,[18] and less consistently with greater focal parenchymal lesion burden on CT imaging,[7,8] Patients with midbrain and pontine lesions are at greater risk of PSH,[26] but incidence is also increased with lesions in the periventricular white matter, corpus callosum, and deep gray nuclei. Most recently, an analysis of diffusion tensor magnetic resonance imaging in 102 patients, 16 of whom had PSH,[34] showed an association of PSH with lesions in the corpus callosum and posterior limb of the internal capsule. Given that the associations with PSH in these studies are all with markers of more severe and/or diffuse injury, it remains unlikely that any one of these lesions specifically drives PSH, and more likely that the development of PSH is associated with the overall burden of injury. These findings support the suggestion[32] that PSH is a complex disconnection syndrome, with a contributory role for learned allodynic hyperresponsiveness (Figure 1).

Several central neurotransmitter systems have been implicated in the maladaptive responses that drive PSH, primarily based on efficacy of specific neuromodulatory interventions (see below). Regardless of these central neurotransmitter changes, there is good evidence that PSH is associated with peripheral catecholamine (and possibly corticosteroid) release (Figure 2a),[14] which may explain the exaggerated responses to non-noxious or mildly noxious stimuli observed in PSH (Figure 2b).[24] This suggests that allodynic hyperresponsiveness develops due to release of higher control, producing 'sympathetic storms'. However, maladaptive spinal cord plasticity is also possible, as seen in the well-researched and related disorder of autonomic dysreflexia following high spinal cord injury.[57] In PSH, similar spinal cord changes appear permanent, with sub-clinical allodynic/sympathetic over responsiveness persisting for at least 5 years post injury.[35]

Fig 3a

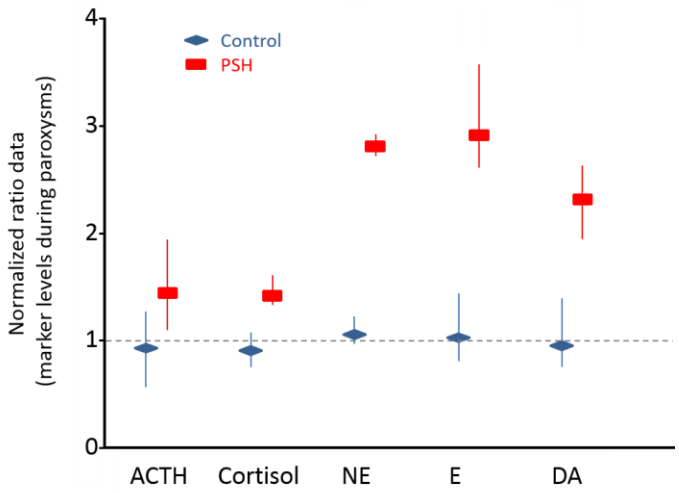

Fig 3b

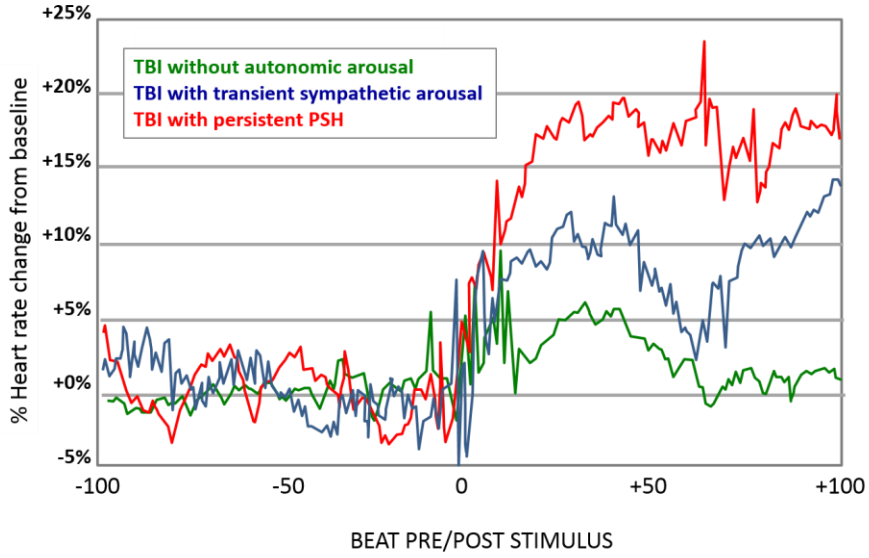

Figure 3.

Pathophysiology of PSH

(A) Median and interquartile range of normalized ratio of marker levels during paroxysms indexed to baseline levels**.** Control medians are blue diamonds and PSH patients are red boxes; all comparisons between these two patient groups are highly significant ($p < 0.001$) for all markers shown. ACTH: Adrenocorticotrophic hormone; NE: norepinephrine; E: epinephrine; DA: dopamine. (Replotted using data originally published in Reference 14[14]. (B) Heart rate responses in PSH. Heart rate responses (plotted as change from baseline) are shown following stimulation in patients recovering from traumatic brain injury who have normal autonomic responses (green), transient sympathetic arousal (blue; which subsides rapidly), and paroxysmal sympathetic hyperactivity (red) with persistent increased sympathetic response to non-noxious stimuli. Panel B is redrawn from data originally reported in Reference 24[24].

Therapeutic options

The three main goals in treatment of PSH are: to avoid the triggers that provoke the paroxysms, to mitigate the excessive sympathetic outflow, and to address the impact of PSH on other organ systems through supportive therapy. In most cases, the level of evidence for these therapeutic options is low, consisting of case reports or small case series, with efficacy reported in terms on anecdotal decreases in sympathetic hyperactivity. No randomized clinical trials (RCTs) have been conducted to date. Whether these interventions influence the long-term outcome in severely brain injured patients suffering from PSH is unclear.

Treatments aimed at PSH may either be aimed at prevention of paroxysms, or aimed at aborting paroxysms that do occur. A range of pharmacological interventions have been used for both these purposes, with incomplete and varying efficacy. These are summarized in Table 3. Though individual agents are thought to have a greater or lesser effect on individual components of the syndrome, this demarcation is far from clear cut, and no agent is universally, or even predictably, effective. In practice, most patients require treatment with multiple agents with potentially complementary roles – both in terms of different components of the syndrome, but also to combine drugs aimed at preventing and treating paroxysms. Individual drugs and drug combinations are typically chosen on the basis of local custom, rather than objective evidence.

The majority (~80%) of PSH paroxysms occur as allodynic responses to external stimuli such as pain, urinary retention, or movement in both clinical[8] and experimental settings.[24] Where triggers can be identified (or suspected), it makes sense to attempt to treat or avoid them [36]. Opioids, especially morphine, are probably the most frequently used, and often first line agents, to suppress the allodynic response in PSH patients.[37] Morphine may also have non-analgesic effects through modulation of central pathways involved in PSH paroxysms. Other opioids and routes of administration, such as fentanyl patches, have also been used.[38] In general, the duration of opioid therapy depends on the duration and severity of PSH symptoms, balanced against the desire to avoid chronic opioid use, but often extends to the rehabilitation phase. Other sedatives, such as midazolam, have also been used in this context. Although haloperidol has been used in the past, there is concern that it may impact adversely on eventual outcome. Gabapentin, often used to treat neuropathic pain, has well-documented effects on presynaptic voltage-gated calcium channels in the dorsal horn of spinal cord, and has been used in PSH unresponsive to metoprolol/bromocriptine.[39]

Alpha-2-adrenergic agents act through central as well as peripheral suppression of adrenergic outflow. In addition, they have an imidazole receptor effect. In PSH, clonidine reduces heart rate, blood pressure and circulating catecholamines, but appears to be less effective in controlling temperature. It may be less appropriate for paroxysmal symptoms, since it may potentiate hypotension and bradycardia between paroxysms, making titration challenging.[36] However, clonidine patches can be effective in controlling the storms, even late in the course of the patient [40]. Dexmedetomidine has also been reported to be effective in managing PSH in the ICU [41,42].

A third class of drugs used in the treatment of PSH symptoms are non-selective beta-blocking agents. Propranolol is probably the most frequently used beta-blocker for this indication, and has the advantage of lipophilicity, which facilitates blood brain barrier penetration and central action. Schroeppel[43] demonstrated that propranolol use was independently associated with lower mortality. Beta-blockers also reduce the metabolic rate, which is often elevated.[44,45] Cardio-selective beta-blockers such as metoprolol are probably less effective; combined alpha- and beta-adrenergic blockade may be better suited to controlling paroxysms.[46] The ongoing double-blind RCT 'Decreasing Adrenergic or Sympathetic Hyperactivity After Traumatic Brain Injury' (DASH after TBI), compares combination therapy with propranolol and clonidine versus placebo in the ICU.[47]

Other modulators of sympathetic paroxysms include the dopaminergic D_2-agonist bromocriptine, which is variably effective in reducing temperature and sweating.[32,36] Baclofen, a GABA-B agonist active at inhibitory interneurons in the spinal cord, has been used for refractory cases, and in three small prospective observational trial, continuous intrathecal Baclofen (100-200 mcg/day) was able to mitigate the course of PSH.[48–50] Dantrolene, used in the treatment of malignant hyperthermia, may work in PSH through reducing intracellular calcium, with a main effect on posturing.[36] A small case series from China reported a possible effect of hyperbaric oxygen therapy on paroxysms and posturing in early subacute PSH, after limited success with medical management [51].

Table 2. Drugs used for treatment (Rx) and prevention (Px) of PSH

Class	Drug	Prophylaxis (Px) or Treatment (Rx). Dose, route (see notes, below)	Site of action	Clinical features targeted	Evidence of efficacy	Cautionary notes
Opioids	Morphine (or other opioids; doses provided are for morphine)[37]	Rx: 1-10 mg bolus IV. Px: IV infusion, titrated to effect	Opioid receptors in brain, spinal cord, (± periphery)	Most features; particularly hypertension, allodynia, tachycardia	Consistent	Respiratory depression, tolerance and dose escalation
	Fentanyl[38]	Px: Patch: 12-100 mcg/h				
Intravenous anaesthetics	Propofol	Rx: 10-20 mg bolus IV Px: IV infusion; max < 4 mg/kg/h	GABA-A receptors in brain	Most features	Consistent	Only if mechanically ventilated, in acute phase
β-adrenergic blockers	Propranolol[43-45]	Px: 20-60 mg 4-6 hourly, PO (Rectal administration also described)	Non-selective β adrenoceptor blocker (central, cardiac, peripheral)	Tachycardia, hypertension, diaphoresis May help with dystonia	Consistent	Bradycardia, hypotension, bradyarrhythmias, sleep disturbances, masked hypoglycaemia, especially with oral antidiabetics
	Labetalol[46]	Px: 100-200 mg 12 hourly, PO	β and α adrenoceptors		Limited	
	Metoprolol	Px: 25 mg 8 hourly, PO	Cardioselective B adrenoceptors	Limited or no impact	Ineffective	
α -2 agonists	Clonidine[36]	Px: 100 mcg 8-12 hourly PO; titrate to maximum1200 mcg/day. Px: IV infusion, titrate to effect	α -2 adrenoceptors in brain and spinal cord	Hypertension and tachycardia	Intermediate	Hypotension, bradycardia, sedation; IV infusions not a long term solution, but clonidine patches may be useful.[40]
	Dexmedetomidine[41,42]	Px: IV infusion titrate to effect 0.2-0.7 mcg/kg/h				
Neuromodulators	Bromocriptine[32,36]	Px: 1.25 mg PO 12 hourly; max 40 mg/day	Dopamine D2 receptor agonist	Inconsistent	Intermediate	Confusion, agitation, dyskinesia, nausea, hypotension
	Gabapentin[39]	Px: 100 mg 8 hourly PO; max 4800mg/day	α2δ presynaptic voltage gated Ca^{++} channels (in brain/spinal cord)	Spasticity, allodynic responses	Consistent	Well tolerated
	Baclofen[48-50]	Px: 5mg 8 hourly PO; max 80 mg/d Px: Intrathecal – specialist use only	GABA-B agonist	Spasticity, dystonia	PO: Limited; IT: Consistent	Sedation, withdrawal syndrome

Benzodiazepines	Diazepam, Lorazepam Midazolam Clonazepam	Rx: 1-10 mg IV boluses Rx: 1-4 mg IV boluses Rx: 1-2 mg IV bolus Px: 0.5 – 8 mg/d PO in divided doses	Central benzodiazepine receptor on GABA complex (brain and spinal cord)	Agitation, hypertension, tachycardia, posturing	Intermediate Intermediate	Sedation; IV boluses with caution in subjects without secure artifical airway
Sarcolemmal Ca^{++} release blocker	Dantrolene[36]	Rx: 0.5 -2 mg/kg IV 6-12 hourly; maximum 10 mg/kg/day	Blocks sarcolemmal Ca^{++} release in muscle	Posturing and muscular spasm	Intermediate	Hepatotoxicity, respiratory depression

Notes to Table 2:

- Drug administration routes are intravenous (**IV**) or per orally (**PO**; which includes administration through a nasogastric or other feeding tube). Drug doses and impressions of efficacy are indicative, based on past publications (cited in the text[36-51]), and are largely covered in five reviews on the subject. [3, 36,54, 58]
- The dose ranges listed in the table cover the entire range that have been reported in the literature. <u>These data are provided as a record of what has been published, rather than as a recommendation for treatment.</u> Please ensure that the dosage and route of administration of drugs used in patients take account of individual circumstances and good clinical practice.
- Evidence of efficacy is described as **Consistent** (benefit in many/most of the publications reviewed); **Intermediate** (where there is equivocal impression of benefit in the literature), **Limited** (when the data are limited and inconclusive, but show some benefit), or **Ineffective** (when the literature shows no benefit).
- These judgements are necessarily subjective – a formal meta-analysis is not possible as the literature is very heterogeneous and poorly documented. Not all published case reports are included, but drug classes, and specific agents, that have been commonly tried for PSH are covered in this table.
- Combinations of drugs are commonly employed in clinical practice – combining interventions for both prevention and treatment of paroxysms, and using drugs in different therapeutic classes with different mechanisms. These drugs and drug combinations are based on local custom, rather than objective evidence.

Supportive therapy to deal with the consequences of PSH is extremely important. Physiotherapy, paying attention to positioning of the patients to prevent contractures, and managing temperature are crucial. Nutritional management deserves special attention: dramatic increases in resting energy expenditure (REE), up to threefold baseline, have been reported during paroxysms,[11] and some PSH patients admitted to rehabilitation units show significant weight loss of up to 25-29% following ICU management.[52] Indirect calorimetry can guide calorie intake in proportion to increased REE. PSH increases the relative risk (RR) of heterotopic ossification (RR= 59.6, 95% CI=8.4–422),[10] and this diagnosis should be considered in all patients with hot or painful joints.

Conclusions and research agenda

PSH is an intriguing clinical syndrome, that occurs after severe acquired brain injury of multiple etiologies, but most prevalent after TBI and hypoxic brain injury. Recent initiatives to define PSH with clinical criteria are the first steps in a longer journey to study the causes, consequences, and potential therapies for this condition. Potential therapeutic agents may suppress manifestations of PSH, but no prospective RCTs have been published regarding the potential benefits, risks, or outcome impacts of such intervention.

The advances in clinical tools for diagnosis characterization of PSH are based on a wide clinical consensus, and involve most active investigators in the field. However, linking these clinical features to lesion location and severity, and to clear neuropathology, remains challenging, in large part due to variable pathophysiology (and hence) treatment response. Stratifying the syndrome into mechanistically homogeneous subgroups with common pathophysiology, diagnostic features, therapy response and outcome is essential if we are to pursue precision medicine approaches to its management. However, accumulating the large cohorts of patients to allow such stratification is challenging. Despite recent diagnostic criteria, the description of patients seems to be varied and inconsistent, especially in terms of imaging findings, therapies and outcome. The use of common data elements for such description, borrowed from acute TBI research, and modified if needed, may represent one means of addressing this issue. This approach would also allow us to define assessment tools and timings for defining early and late outcome, thus enabling a more rigorous epidemiological assessment of the incidence of PSH and its impact on outcome. Finally, there is a need for pragmatic, but well conducted clinical trials of therapies, either individually, or in sequence (in an escalation pattern) to confirm or refute the putative benefit reported in case series or small trials. Such studies will demand multicenter recruitment, which could make use of existing collaborative research networks that focus on PSH.

Contributors:

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Declarations of interest:

GM and IJB declare no competing interests.

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Search strategy and selection criteria

This manuscript builds on an exhaustive review undertaken by the same group of authors in 2010.[1] We conducted a search on MEDLINE (January 1st, 1946 to June 21st, 2017) using the following terms:

> *(PSH OR diencephalic epilepsy OR storm OR paroxysmal sympathetic hyperactivity OR dysautonomia) AND (diagnosis OR definition OR treatment OR pathophysiology OR outcome) AND (brain injury OR stroke OR cardiac arrest OR head injury OR traumatic brain injury OR subarachnoid haemorrhage OR intracerebral haemorrhage) NOT (tumors OR neoplasms OR Parkinson's OR familial)*

This search yielded 975 hits, titles of which were manually searched for relevance to our review topic. The abstracts of the resulting 67 manuscripts were reviewed in addition to 115 manuscripts that had been identified during our search in 2010 (with considerable overlap between the two). The abstracts of these manuscripts and manuscripts selected for review of full text by one or more of the authors, and papers selected for inclusion in this review. No attempt was made to undertake a fully systematic and inclusive review.

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Paroxysmal Sympathetic Hyperactivity: the storm after acute brain injury

Supplementary material

Supplementary Table 1: Clinical items contributing to a diagnosis of PSH

Supplementary Table 2: The Paroxysmal Sympathetic Hyperactivity Assessment Measure

Supplementary Table 3: Pediatric Paroxysmal Sympathetic Hyperactivity Scoring Reference

Supplementary Table 1. Clinical items contributing to a diagnosis of PSH

1. Antecedent acquired brain injury
2. Simultaneity of clinical features
3. Clinical features are paroxysmal in nature
4. Sympathetic over reactivity to normally non-painful stimuli
5. Absence of intra-paroxysmal parasympathetic features during episodes
6. Medication is administered to decrease sympathetic features
7. Lack of alternative explanations
8. Features persist despite treatment of alternative differential diagnosis
9. Features persist ≥ 3 consecutive days
10. Features persist ≥ 2 weeks post-injury
11. (Frequency of ≥ 2 episodes per day)

Supplementary Table 2: The Paroxysmal Sympathetic Hyperactivity Assessment Measure

Component	*Score*	0	1	2	3	Allocated score
Clinical Feature Scale (CFS)	Heart rate (per min)	<100	100-119	120-139	≥140	
	Respiratory rate (per min)	<18	18-23	24-29	≥ 30	
	Systolic blood pressure (mmHg)	<140	140-159	160-179	≥180	
	Temperature (^{0}C)	<37.0	37.0-37.9	38.0-38.9	≥39.0	
	Sweating	Absent	Mild	Moderate	Severe	
	Posturing during episodes	Absent	Mild	Moderate	Severe	
	CFS subtotal *(Severity: 0 = Nil; 1-6 = Mild; 7-12 = Moderate; ≥ 13 = Severe)*					
Diagnosis Likelihood Tool (DLT)	Antecedent acquired brain injury					
	Clinical features occur simultaneously					
	Episodes are paroxysmal in nature					
	Sympathetic over-reactivity to normally non-painful stimuli					
	Absence of parasympathetic features during episodes					
	Features persist > 3 consecutive days					
	Features persist ≥ 2 weeks post-brain injury					
	≥ 2 episodes daily					
	Absence of other presumed causes of features					
	Features persist despite treatment of alternative differential diagnoses					
	Medication administered to decrease sympathetic features					
	DLT Subtotal *(Score 1 point for each feature present)*					
PSH-Assessment Measure (PSH-AM = CFS subtotal + DLT subtotal)						

	Score	PSH diagnosis
Interpretation of PSH-AM (CFS subtotal + DLT subtotal)	<8	Unlikely
	8-16	Possible
	≥ 17	Probable

Supplementary Table 3: Pediatric Paroxysmal Sympathetic Hyperactivity Scoring Reference				
Score	**0**	**1**	**2**	**3**
1-4 years				
Heart rate (per minute)	<110	110-124	125-139	≥140
Respiratory rate (per minute)	<30	30-34	35-39	≥40
Systolic blood pressure (mmHg)	<100	100-109	110-119	≥120
Diastolic blood pressure (mmHg)	<65	65-72	73-79	≥80
Temperature (°C)	<37.0	37.0-37.9	38-38.9	≥39.0
Sweating	Normal	Increased sweating	Localized diaphoresis	Generalized diaphoresis
Muscle tone increase	Absent	Mild increase	Neat increase	Generalized spasticity or opisthotons
5-15 years				
Heart rate (per minute)	<100	100-119	120-139	≥140
Respiratory rate (per minute)	<25	25-29	30-34	≥35
Systolic blood pressure (mmHg)	<120	120-129	130-139	≥140
Diastolic blood pressure (mmHg)	<75	75-82	83-89	≥ 90
Temperature (°C)	<37.0	37.0-37.9	38-38.9	≥39.0
Sweating	Normal	Increased sweating	Localized diaphoresis	Generalized diaphoresis
Muscle tone increase	Absent	Mild increase	Neat increase	Generalized spasticity or opisthotons

This table is reconstructed based on data from Pozzi et al, Journal of Neurotrauma 2014; 31: 1897–98