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European Journal of Medical Research (2025) 30:349
https://doi.org/10.1186/s40001-025-02564-w

European Journal
of Medical Research

REVIEW

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Diagnosis and management of paroxysmal sympathetic hyperactivity: a narrative review of recent literature

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Abstract

Paroxysmal sympathoexcitatory syndrome is a clinical 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. Coupled with the absence of uniform treatment guidelines, it is prone to underdiagnosis and misdiagnosis, leading to the adoption of inappropriate treatment protocols, which may adversely affect the prognosis of patients. This narrative review summarized the existing literature and provided a comprehensive account of the research history and terminology of PSH, epidemiology and pathogenesis, diagnostic criteria, therapeutic options, and prognosis, hoping to bring new ideas to the clinical treatment of PSH.

Keywords PSH, Epidemiology, Diagnosis, Treatment

Introduction

Paroxysmal sympathetic hyperactivity (PSH) is a severe clinical 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 [1]. The clinical history of PSH is complex, and at least dozens of names are used to describe this syndrome. After joint research and discussion among international experts, PSH was identified as the best term to describe this syndrome [1, 2]. Currently, the diagnostic criteria for paroxysmal sympathetic nerve excitation syndrome are unclear, and its clinical manifestations are not specific, making it easy to be confused with other diseases. In addition, there is no unified treatment guideline, which makes it easy to be underdiagnosed and misdiagnosed and then take inappropriate treatment plans, which may cause adverse effects on the prognosis of the patients and may even lead to the patient's deaths [3, 4]. The academic community has not definitively determined the pathogenesis of PSH, and more clinical and experimental studies are needed to explore it and better serve the clinic. The treatment of PSH is currently empirical, with a variety of therapeutic options, the effects of which are unclear, and some special therapies have also been applied by physicians in the clinical treatment of patients with PSH [5]. Given the difficulties in diagnosis and treatment of PSH, this article summarizes the articles on PSH in recent years, mainly discussing the research history and terminology of PSH, etiology and pathogenesis, diagnostic criteria,

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and therapeutic options, with the hope of bringing new ideas and thoughts to the clinical work and improving the prognosis of patients.

Methods

This paper is a narrative review. The Web of Science, PubMed, Cochrane Library, and CNKI databases were searched by computer. Search terms included paroxysmal sympathetic hyperactivity, sympathetic storm, dysautonomia, for the period 2014–2024. The main objectives of the literature search were to research the history and terminology of PSH, epidemiology and pathogenesis, diagnostic criteria, and therapeutic options. A comprehensive overview of PSH was provided after excluding duplicates, case reports, or irrelevant literature.

Research history and naming process

The research history of PSH is relatively short. With the continuous progress of neuroscience and medical research, the understanding of this disease is constantly improving. The earliest observation of PSH can be traced back to the early twentieth century. At that time, doctors began to notice that some patients with brain injury or trauma showed abnormal sympathetic activity, including increased heart rate, increased blood pressure, shortness of breath, and other symptoms. The symptoms of these patients aroused great interest in the medical community at the time, but there was no uniform terminology to describe the disease [6]. Penfield first described the symptoms of autonomic dysfunction in patients with craniocerebral injury in 1929 and named it"diencephalic autonomic epilepsy"[7]. With the development of medical technology and the deepening of clinical research, the medical community's understanding of this syndrome has gradually deepened. Alejandro Rabinstein first coined the name PSH in 2007 [8], and the rest of the scholars have their own research and opinions on this syndrome and have proposed at least 31 different names, such as sympathetic storm, hypothalamic midbrain dysregulation syndrome, paroxysmal sympathetic instability with dystonia, and so on [9]. Ian J. Baguley argued that the confusing nomenclature of PSH prevented further research and that there needed to be more consensus in the medical community as to what the syndrome consisted of. To alleviate this dilemma, in 2014, an international panel of experts, mainly represented by Baguley, formally named this syndrome PSH by studying its previous literature and clinical features [10]. The international panel of experts reached the following consensus on the conceptual definition of PSH: a syndrome found in survivors of severe acquired brain injury in which there is a combination of sympathetic (heart rate, blood pressure, respiratory rate, body temperature, sweating) and motor (postural) activity occur simultaneously with paroxysmal transient enhancement [11, 12].

Epidemiology and pathogenesis

The etiology of PSH is complex; most of them are related to craniocerebral injury, among which traumatic craniocerebral injury (TBI) is the most common [13], and the incidence of PSH varies in different studies. In 2007, Rabinstein's study found that TBI caused 33% of PSH [8], and in 2011, a survey of Perks enrolled a total of 349 patients with PSH, of whom 79.4% were caused by craniocerebral trauma, followed by ischemic–hypoxic encephalopathy (HIE), cerebrovascular disease, brain tumors, hydrocephalus, and intracranial infections [14]. Some reports suggested that neuronal waxy lipofuscinosis (Batten's disease), anti-N-methyl-d-aspartate receptor encephalitis, Guillain–Barré syndrome, and fat embolism syndrome can also cause PSH [15, 16]. In a 2012 case–control study of PSH by Kirk [17], 259 children were enrolled, including 10% with traumatic brain injury and 31% with cardiac arrest. 26 children were enrolled in Pozzi's 2015 study, including 12 with traumatic brain injury, 9 with hypoxic encephalopathy, and 5 with the remaining etiologies [18]. The prevalence of PSH fluctuates widely and may be influenced by the design of the study, the screening criteria, the type and severity of brain injury, the type and severity of brain injury, the choice of diagnostic criteria, publication bias, and other factors.

To clarify the pathogenesis of PSH, various academic theories which have evolved, and these theories generally agree that the occurrence of PSH is related to the loss of inhibition of the sympathetic nervous system and the lack of antagonism of the parasympathetic nervous system, which makes the sympathetic nervous system overactive and challenging to regulate [19].

Epilepsy theory

Epileptic electrical activity in the mesencephalon belonging to the pathogenesis of PSH was one of the first doctrines to be proposed. As early as 1921, Penfield put forward this idea [20], and later, some scholars found that carbamazepine was effective in some patients with tachycardia, elevated blood pressure, shortness of breath, etc. [21]. This finding provides clinical support for the epilepsy theory; however, for some patients with autonomic dysfunction, using antiepileptic treatment failed to achieve the expected results [22]. Therefore, the epilepsy theory, although it may partially explain the

pathogenesis of PSH, has been abandoned due to the lack of strong clinical evidence.

Axonal injury theory

Sympathetic responses are modulated by multiple cortical and subcortical regions, and therefore, diffuse and multifocal brain injuries are prone to PSH. Hinson et al. found that MRI in patients with PSH suggested the presence of brainstem, deep cranial structures, and diffuse axonal injury and that PSH was more likely to occur when white matter bundles in the posterior part of the corpus callosum and posterior limb of the internal capsule were disconnected. Accordingly, it was proposed that diffuse damage to the cerebral white matter tracts interrupting central nerve signaling may be one of the pathogenic mechanisms of PSH [23]. It was also pointed out that projection fibers such as corticospinal tracts and cortico-red nucleus tracts passing through the damaged posterior limb of the internal capsule may be one of the damaged conduction pathways. These findings provide an experimental basis for the establishment of relevant models further to elucidate the physiological mechanisms of PSH through clinical studies.

Neuroendocrine disorders theory

From a neuroendocrine perspective, patients presenting with symptoms such as hypertension, fever, sweating, and tachycardia have been associated with overexpression of hormones such as epinephrine and norepinephrine. Renner proposed that the hypothalamic–pituitary–adrenocortical axis may be a new conjecture to explain the physiological mechanisms of PSH in 2015 [24]. He suggested that the etiology of PSH stems from multiple neurotransmitter alterations and cellular dysfunction and that when trauma, tumors, and other factors affecting brain injury lead to functional impairment of the hypothalamic–pituitary–adrenocortical axis, resulting in a significant secretion of corticotropin releasing hormone in the patient, which may lead to adrenergic receptor hyperactivity and thus induce a stress response, leading to the onset of PSH. The Fernandez-Ortega's study supported the neuroendocrine theory by demonstrating that during episodes of PSH, serum catecholamine levels increased by as much as 300%, while adrenocorticotropic hormone levels rose by approximately 40% in some patients [25]. However, this study failed to provide a strong indication of the relationship between PSH and the adrenocortical axis, and the relationship between PSH and the thyroxine axis was not confirmed. The complex central and peripheral interactions of hormones and their disruption may provide one of the many explanations for the diversity of clinical symptoms of PSH, and more prospective experimental studies are needed to provide experimental support for this idea in the future.

Disconnection theory

The traditional theory of disconnection mechanism suggests that the higher centers located in the cerebral cortex and hippocampus play an inhibitory role in sympathetic activity, while the lower centers located in the brainstem, hypothalamus, and spinal cord play an inhibitory role in sympathetic activity. When the higher centers are damaged, or the connection with the lower centers is interrupted, the lower centers lose their inhibitory regulation and are in a state of hyperexcitability with disconnection and disinhibition, resulting in the production of PSH [26]. Initially, this theory was a good explanation for typical focal and diffuse axonal injuries; however, further research has found that there are major limitations to this theory. The disconnection mechanism theory suggests that excitatory centers exist in the brainstem and mesencephalon, which requires that low-level centers such as the brainstem and their conduction pathways remain structurally intact in patients with PSH, which is inconsistent with the fact that some patients with injuries to the brainstem and other parts of the brainstem can also develop PSH, and this theory cannot well explain the clinical manifestation that the patient overreacts to mild, non-damaging stimuli [27]. Therefore, this theory was gradually discarded, and some scholars, once again, based on in-depth research, proposed the excitatory/inhibitory ratio model theory.

Excitatory/inhibitory ratio model theory

The most widely accepted theory is the excitatory/inhibitory ratio (EIR) model theory, which was first proposed by Baguley in 2007, who, by studying a variety of clinical syndromes presenting with severe autonomic nervous system (ANS) and muscle overactivity, broadly categorized their pathologies into brain-originated and spinal cord-originated disorders [28]. Their mechanisms for neurotransmitter dysfunction or structural damage were noted, and these disorders share a common underlying mechanism, according to which a theoretical structure was proposed: the EIR model theory. The model is based on losing control of normal spinal cord mechanisms and explains different but overlapping disease states within a unified framework. Baguley introduced the concept of EIR to explain symptoms such as sympathetic hyperexcitability and activity. Spinal cord EIR (SEIR) can stage modulate spinal cord responsiveness to a continuous flow of information

from afferent nerves, and brainstem EIR (BEIR) can inhibit spinal cord afferent stimulus reflexes. When brainstem inhibitory centers or their downstream conduction pathways are impaired, this contributes to an increase in the SEIR and feedback inhibition of the BEIR, allowing small, innocuous stimuli to be converted into injurious stimulus signals that are continuously superimposed, ultimately leading to PSH [29].

Diagnosis and differential diagnosis

Clinical features

PSH often presents with episodes of autonomic motor symptoms. Autonomic symptoms are mainly characterized by sympathetic overexcitation, i.e., agitation, profuse sweating, hyperthermia, increased blood pressure, pupil dilatation, accelerated heart rate, and respiration [1, 2]. However, in addition to sympathetic overexcitability, parasympathetic overexcitability may also accompany autonomic symptoms, which are mainly characterized by a slow heart rate, a low respiratory rate, a lack of elevated blood pressure, a low body temperature, pupil constriction, perspiration, and tears, etc. [2, 8, 28]. Episodes of motor symptoms are mainly manifested dystonia, dystonic/cortical tonus, muscle hypertonia, muscle spasms, and myoclonus. These autonomic motor symptoms usually occur 1 week after the brain injury, 1 to 3 times a day, often appear suddenly, last a few hours, and then quickly end; the duration of the disease ranges from 1 to 2 weeks or months [30].

Diagnosis

The diagnosis of PSH mainly relies on medical history and clinical manifestations. Still, its clinical manifestations lack specificity and are similar to or overlap with the manifestations of muscle hypermobility and autonomic hyperexcitability in many neurological diseases, which brings considerable trouble to clinical diagnosis. As quite a few scholars have deepened their knowledge of PSH, its diagnostic criteria have also been constantly updated [31]. Since the publication of the first diagnostic criteria for PSH in 1993, eight diagnostic criteria have been proposed successively, among which those of Blackman, Fernandez Ortega and Rabinstein were more recognized, as detailed in Table 1 [8, 32, 33]. For patients with hypertensive cerebral hemorrhage presenting with PSH, Heffernan thought that such patients were routinely applying antihypertensive drugs to control their blood pressure in clinical practice and that blood pressure as a diagnostic criterion for PSH had a large error. [34]. Therefore, he proposed the diagnostic criteria suitable for PSH after hypertensive cerebral hemorrhage.

Although multiple diagnostic criteria had been raised, some literature found that most cases did not meet the

Table 1 Diagnostic standards

	Clinical characteristics	Definitive diagnosis
Blackman	(1) Temperature ≥ 38.5 °C (2) ≥ 20 breaths/min (3) Agitation (4) Systolic blood pressure ≥ 140 mmHg (5) Severe craniocerebral injury (Rancho Los Amigos level, ≥ IV) (6) Sweating (7) Dystonia (rigid or de-cerebralized tonic postures)	At least five or more criteria are met, the episodes occur at least once per day, last more than three days, and other diseases need to be excluded
Fernandez Ortega	(1) Tachycardia (2) Hypertension (3) Tachypnea (4) Decreased consciousness (5) Dilated pupils (6) Sweating (7) Perspiration (8) Muscle tonus	At least five or more criteria are met, and other diseases need to be excluded
Rubinstein	(1) Fever (2) Tachycardia (3) Tachypnea (4) Hypertension (5) Profuse sweating (6) Dystonia	At least four or more criteria are met and diseases such as sepsis and respiratory obstruction are excluded

Table 2 Clinical Feature Scale (CFS)

	0	1	2	3	Score
Heart rate (beats/min)	<100	100–119	120–139	≥ 140	
Respiratory rate (breath/min)	<18	18–23	24–29	≥ 30	
Systolic blood pressure (mmHg)	<140	140–159	160–179	≥ 180	
Temperature(℃)	<37.0	37.0–37.9	38.0–38.9	≥ 39.0	
Sweating	Nil	Mild	Moderate	Severe	
Posturing during episodes	Nil	Mild	Moderate	Severe	

Table 3 Diagnosis Likelihood Tool (DLT)

Score 1 point for each feature present
Clinical features occur simultaneously
Episodes are paroxysmal in nature
Sympathetic over-reactivity to normally non-painful stimuli
Features persist ≥ 3 consecutive days
Features persist ≥ 2 weeks post -brain injury
Features persist despite treatment of alternative differential diagnoses
Medication administered to decrease sympathetic features
≥ 2 episodes daily
Absence of parasympathetic features during episodes
Absence of other presumed cause of features
Antecedent acquired brain injury

above criteria, which showed that these diagnostic criteria did not serve well in clinical work [14]. The international steering committee represented by Baguley simplified the nine diagnostic criteria through the Delphi method and, after several rounds of consultation, proposed new diagnostic criteria and released a new research tool: PSH-AM [2, 35]. PSH-AM consists of two main parts: one part evaluates the severity of the clinical features (Clinical Feature Scale (CFS)), and the other part deals with the probability of diagnosis ((the Diagnosis Likelihood Tool (DLT)). The numerical outputs of these two components were summed to estimate the likelihood of diagnosing PSH at that point in time. The CFS, by summarizing the relevant literature, proposed six core clinical symptoms, such as tachycardia and hyperthermia, which were assigned scores according to their severity, with lower scores being closer to normal and higher scores being more severe in terms of the clinical manifestations (for details, see Table 2). The DLT proposes 11 clinical features for assessing the likelihood of a PSH episode, with each feature scoring one if present and 0 if absent, and the higher the score, the greater the likelihood of PSH (see Table 3 for details). Combined CFS and DLT were used to determine the likelihood of diagnosing PSH: unlikely to diagnose (< 8 points), likely to diagnose (8–16 points), and very likely to diagnose (≥ 17 points), as detailed in Table 4. The study showed that PSH-AM improved the clinicians'diagnosis of PSH and facilitated the assessment of patients with brain injury who might have PSH, with a diagnostic sensitivity of up to 94% [36]. Some scholars have pointed out that PSH-AM also has shortcomings; CFS does not take into account some clinical extremes, severe agitation patients with large fluctuations in blood pressure and temperature, and other clinical characteristics, which cannot be accurately recorded, increasing the diagnostic error [37]. In addition, some pediatricians have pointed out that pediatric patients may present only with elevated diastolic or systolic blood pressure and may have episodes once a day for more than a week, requiring separate evaluation [38]. Therefore, the diagnostic criteria for PSH still need to be further improved and standardized to guide clinical work better.

Differential diagnosis

The clinical symptoms of PSH have no apparent specificity, and it is required to differentiate it from other diseases that can cause fever, sweating, dystonia, and other symptoms. (1) Autonomic epileptic seizure: mainly through the distribution of lesions, diagnostic methods, imaging manifestations and other aspects of differentiation and PSH, see Table 5. (2) Central fever: non-infectious fever caused by the thalamus or brainstem and other central nervous system lesions caused by the central thermoregulatory center abnormality, and the difference with the PSH is that the clinical manifestations of the majority of the fever for the retention of fever,

Table 4 PSH composite scoring criteria

Degree	Mild	Moderate	Severe
(CFS)	0–6	7–12	≥ 13
Diagnosis	**Unlikely**	**Possible**	**Probable**
(CFS + DLT)	0–7	8–16	≥ 17

Table 5 Differentiation of PSH and phyletic epilepsy

Features	PSH	Autonomic epileptic seizure
Lesion distribution	Diffuse	Focal
Stereotype episode	Yes	No
Diagnostic methods	PSH-AM	EEG
Antiepileptic treatment	Lack of effectiveness	Validity
β-Blocker therapy	Validity	Lack of effectiveness

usually not accompanied by sweating, respiration and rapid pulse and other heat dissipation response, the use of antibiotics and antipyretics is not effective. (3) Infectious fever: fever caused by various pathogenic bacteria entering the human body, resulting in the release of endogenous pyogenic sources, the existence of primary foci of infection, experimental testing can be found in PCT, CD64, PCT, and other indicators of infection, the use of antibiotics is adequate. Some rarer and easily confused diseases have also been reported abroad, such as antipsychotic drug-induced severe adverse reaction malignant syndrome, hyperthyroidism crisis, and withdrawal syndrome. [39, 40].

Treatment

Currently, there is no standardized treatment protocol for PSH treatment, and most of the literature reports empirical treatment. The aims of PSH treatment include the following three main types: avoidance or reduction of PSH-inducing stimuli, alleviation of excessive sympathetic arousal, and symptomatic supportive treatment to reduce the damage caused by PSH to other organ-activated systems. To achieve the therapeutic objectives, PSH treatment can be summarized into three aspects: non-pharmacological treatment, drug treatment, and special treatment [41].

Non-pharmacological treatment

Patients with brain injury have a hyperfunctioning brain and increased energy demand, and the energy demand is higher during PSH episodes. Monitoring patients'nutrition, hydration, and electrolyte changes to maintain the stability of the internal environment can improve patients'prognosis. Clinical studies advocate early enteral nutrition and commonly used feeding methods include percutaneous endoscopic-guided gastrostomy, gastrostomy tube, jejunal feeding tube, etc. [42]. During PSH episodes, to minimize the stimulation of the patient, the number of turnovers and suctioning will decrease significantly, and it is straightforward to develop hypostatic pneumonia. During an attack, high blood pressure, fast heart rate, and shortness of breath will adversely affect the heart and respiratory system. At the same time, the combined application of multiple medications will bring about different degrees of toxicity to the liver, kidneys, and respiratory system. Therefore, while controlling the symptoms of PSH, the function of all organs in the body should be closely monitored to prevent and control complications such as hepatic insufficiency, renal insufficiency, pneumonia, respiratory failure, etc. Moreover, family education and support are essential aspects of the individualized management of patients with PSH. Salmani and Harmon-Jones found that emotional stimulation by loved ones could promote arousal and consciousness recovery in craniosynostosis patients [43, 44]. A controlled clinical study found that sensory stimulation by the patient's family was more effective than the same intervention by the charge nurse in promoting the patient's awakening. Patients with PSH have severe and recurring symptoms, long treatment times, and a high burden of care. More attention should be paid to the psychological stress and care needs of the companions, and more assistance should be provided to improve the quality of care [45].

Drug therapy

The mechanism of pharmacological treatment of PSH is mainly to act on target cell surface proteins, including opioid receptors, γ-aminobutyric acid (GABA) receptors, dopamine receptors, voltage-gated calcium channels, α-adrenergic receptors, β-adrenergic receptors, etc., and to exert their effects by inhibiting the hypersensitivity response of afferent sensory pathways, inhibiting central neurotransmitter transmission, and blocking end-targeted organs from responding to sympathetic nerves [46]; see Table 6 for details.

β-Blocker

β-Blockers control the frequency of PSH episodes and reduce their symptoms by antagonizing sympathetic and catecholamine transmitters through central β-receptors. The commonly used drug is propranolol, which is a non-selective β-blocker with good lipophilicity and permeability, easy to pass the blood–brain barrier, and can effectively control blood pressure and reduce heart rate. Not only that, propranolol can interact with lidocaine, colistin, fentanyl, etc., but we need to pay attention to the adverse effects of the drug combination. Labetalol is an antihypertensive drug with both α-blocker and β-blocker effects, and some studies have found that it is effective in relieving hypertension, tachycardia, and other symptoms [47]. At the same time, selective β-blockers metoprolol and atenolol have no significant efficacy in PSH patients [48]. When applying β-blockers, it is necessary to pay attention to and avoid the side effects such as

Table 6 Pharmacological treatment of PSH

Types	Typical drugs	Mechanism of action	Therapeutic effects	Side effects
β-Blocker	Propranolol	Antagonism of sympathetic and catecholamine transmitters	Control blood pressure and lower heart rate	Bradycardia, hypotension, hypoglycemia
α2 agonist	Dexmedetomidine	Agonizes α2 receptors in central and peripheral sympathetic nerves and decreases sympathetic efferents	Sedative, lowers blood pressure, slows heart rate	Bradycardia, chest tightness, hypotension
Opioid agonist	Morphine	Inhibition of central sympathetic excitatory efferents	Analgesic, lowers blood pressure, slows heart rate	Drug dependence, bloating, respiratory depression
$GABA_A$ agonist	Benzodiazepine	Binds to $GABA_A$ receptors and inhibits the release of neurotransmitters such as catecholamines	Anxiolytic, antiepileptic, anticonvulsant, muscle relaxant and sedative-hypnotic	Drug dependence, drowsiness
$GABA_B$ agonist	Baclofen	Activation of $GABA_B$ receptors and inhibition of excitatory amino acid neurotransmitter release	Analgesic, muscle relaxant	Drowsiness, nausea, bloating, low blood pressure
GABA derivative	Gabapentin	Binds calcium channels and reduces excitatory neurotransmitters and impulse efferents	Anticonvulsant, analgesic	Vertigo, drowsiness, headaches
Dopamine agonist	Bromocriptine	Acts on sympathetic ganglia and adrenergic nerve endings, decreasing adenylate cyclase activity and dopamine release	Relieves myasthenia gravis, lowers blood pressure, lowers heart rate, lowers temperature	Chest pain, dyspnea, hypotension, nausea, arrhythmia
Muscarinic	Dantrolene	Inhibition of calcium ion release from sarcoplasmic reticulum	Loosen muscles	Liver damage, respiratory depression
Medicinal plant	Wild carrot	Alkaloids, carbohydrates	Analgesic, anti-inflammatory	Potential organ damage

bradycardia, hypoglycemia, and hypotension produced by them.

α2 agonist

By activating α2-adrenergic receptors, α2-agonists block sympathetic efferents from the hypothalamus and ventral medulla oblongata, lowering peripheral vascular resistance and decreasing the concentration of catecholamines in the blood, thereby controlling symptoms such as tachycardia and hypertension. Representative drugs are colistin and dexmedetomidine. Colistin can effectively prevent the symptoms of PSH, such as increased blood pressure and tachycardia, and play a specific sedative effect through the negative feedback mechanism. Still, when used alone, it is not adequate for other symptoms of PSH, such as increased body temperature and dystonia, etc. Dexmedetomidine is the most effective drug in clinical practice. Dexmedetomidine is the most widely used α2 agonist in clinical practice and has attracted much attention from scholars because of its sedative, analgesic, and anxiolytic effects and its insignificant inhibitory effect on respiration [49]. Tang et al. found in a retrospective study that dexmedetomidine had a positive preventive effect on the emergence of PSH in patients with postoperative traumatic brain injury [50]. In a controlled clinical study, Peng et al. found dexmedetomidine superior to propofol in managing symptoms such as increased blood pressure, increased heart rate, shortness of breath, and hyperthermia in patients with PSH [51]. Guanfacine is the world's first selective α2 agonist, which can directly bind to receptors in the prefrontal cortex. Miyoshi et al. used guanfacine in combination with gabapentin to treat a 60-year-old patient with PSH, and the patient's prognosis improved significantly, which provides a new idea for the treatment of PSH and needs to be further investigated in the clinic [52].

Opioid agonist

Opioid agonists act on μ-opioid receptors in the brain and spinal cord to modulate autonomic reflex pathways and inhibit central sympathetic output. The most frequently used drug is morphine, followed by fentanyl and codeine. Morphine is effective in analgesia, lowering blood pressure, slowing heart rate, etc., and is used to control the onset of PSH symptoms terminally [53]. Raithel et al. found that the early use of morphine was effective in preventing the clinical symptoms of PSH, and this conclusion is supported by the literature, which states that morphine is clinically more effective than other opioids [54]. However, the existence of drug

dependence on morphine can also lead to respiratory depression, intestinal obstruction, and other adverse reactions; some scholars pointed out that the use of fentanyl patches partially replaces the use of morphine. Despite a series of adverse effects, the use of opioids is still clinically recommended until the patient's recovery stage [55].

GABA receptor agonists and their derivatives

GABA is a non-protein amino acid that is the primary inhibitory neurotransmitter in the central nervous system. It modulates neural activity by interacting with GABAA and GABAC receptors, as well as metabotropic GABAB receptors, which regulate the flow of ions across the cell membrane, producing physiological effects [56]. Agonists of GABA receptors and their derivatives effectively alleviate clinical symptoms in patients with post-stroke hemiplegia (PSH) by enhancing the function of GABA receptors.

Benzodiazepines are the essential drugs acting clinically on GABAA receptors, producing pharmacologic effects such as anxiolytic, antiepileptic, anticonvulsant, myorelaxant, and sedative-hypnotic by increasing the frequency of chloride channel opening. Its representative drugs are midazolam, clonazepam, diazepam, etc. For patients with acute attacks of PSH, it is recommended to use short-acting benzodiazepines such as midazolam and triazolam and then gradually transition to longer-acting drugs such as diazepam after the symptoms improve [57, 58]. Some scholars have pointed out that in the rehabilitation stage of PSH patients, the use of lorazepam can not only be anxiolytic and sedative, but also relax the muscles and improve the prognosis of patients. Long-term use of benzodiazepines tends to produce drug dependence, and dosage control is recommended for clinical use to avoid adverse consequences [59].

As a GABAB receptor agonist, baclofen promotes the release of inhibitory neurotransmitters and has been used clinically to relieve tonic spasticity and dystonia in PSH [60]. Oral baclofen is less effective in PSH, but intrathecal baclofen can inhibit the activity of spinal interneurons, with anti-myalgia and analgesic effects [61]. Dario found that intrathecal baclofen continuously pumped can mainly alleviate the symptoms of myalgia and muscle stiffness, which is similar to the findings of Hoarau et al. [62, 63]. It is worth noting that intrathecal baclofen injection is an invasive procedure with risks of cerebrospinal fluid leakage and intracranial infection, making intracerebroventricular baclofen injection a safer alternative [64]. Furthermore, Akcil found that baclofen, in combination with fentanyl, dexmedetomidine, and morphine, was effective in improving the symptoms of PSH patients [65].

Gabapentin, a derivative of GABA, blocks excitatory signaling and has been clinically used for pain relief and seizure control [66]. Oral gabapentin dosage has a wide range of choices and needs to be adjusted according to different diseases, different patients'responses, and tolerance [67]. Baguley believes that gabapentin, in combination with other drugs such as morphine, propranolol, midazolam, baclofen, etc., can effectively control the symptoms of autonomic abnormality, and its effect on dystonia and spasticity is noticeable and can be applied in the long term [22]. The most common adverse effects of gabapentin are vertigo and drowsiness, but also weight gain or headache symptoms and even acute hemorrhagic pancreatitis [68].

Dopamine D2 agonist

Dopamine D2 agonists mainly act on sympathetic ganglia and adrenergic nerve endings, which can reduce dopamine release by lowering adenylate cyclase activity, thus alleviating the symptoms of dystonia, tonicity, and hypertension in patients. Bromocriptine is a representative drug of dopamine D2 agonist, which can not only relieve myotonia, lower blood pressure, and lower heart rate, but also control the symptoms of hyperthermia, which is related to its ability to act directly on the hypothalamic thermoregulatory center [69]. Some research discovered that bromocriptine, in combination with other drugs, especially morphine, its efficacy is significantly enhanced by the use of nausea, vomiting, hypotension, and other adverse reactions [70].

Skeletal muscular relaxants

Skeletal muscle relaxants reduce muscle tone and relaxation through their pharmacological effects to alleviate spasticity and tonicity in patients with PSH. Dantrolene can inhibit the release of calcium ions from the sarcoplasmic reticulum and weaken muscle contraction to achieve the therapeutic purpose; due to its substantial hepatotoxicity, respiratory depression, and other adverse effects, the use of patient needs to be closely observed for changes in liver function and vital signs.N2 cholinergic receptor blocking drugs can selectively act on the N2 receptors on the membrane of the motor nerve endplate, blocking the transmission of nerve impulses to the skeletal muscles and leading to muscle relaxation. Commonly used drugs are vecuronium bromide, succinylcholine, etc. [71]. Some

studies have pointed out that it can be combined with fentanyl, midazolam, etc., to enhance the efficacy of the drug [41].

New possibilities for drug therapy: natural medicinal plants

Thakur argued that chemically synthesized drugs for the treatment of PSH are more specific in their mode of action and suffer from various adverse effects. He proposed using natural medicinal plants or phytopharmaceuticals to treat PSH because natural medicinal treatments have been progressively accepted by clinical practice due to their wide range of complementary or synergistic effects on physiological systems, with fewer side effects [72]. They synthesized the relevant literature, proposed ten medicinal plants represented by artichoke, bottle gourd, and Houpoea magnolia, and elaborated on their chemical compositions, pharmacological activities, and biological experimental results. Although the lack of appropriate botanical knowledge, incorrect collection procedures, improper dose management, and other behaviors will bring corresponding adverse consequences, Thakur believes that a single therapeutic measure is not sufficient to deal with the complex physiopathological mechanisms behind PSH effectively and that medicinal plants have a broad application and research potential, and that, under the premise of ensuring the safety of the medicinal plants, it is encouraged to carry out clinical drug experiments or We encourage clinical drug trials or biomedical research on drug plants to ensure safety and bring new directions for the treatment of PSH.

Special therapy

Hyperbaric oxygen therapy can increase blood oxygen content, enhance oxygen diffusion ability, improve microcirculation, and promote collateral circulation establishment, which aids in repairing damaged brain cells and strengthening neurological function. Some studies suggest that hyperbaric oxygen therapy can alleviate most PSH symptoms and reduce recurrence rates in patients with poor medication response. However, further clinical research is necessary to confirm its efficacy, given the sample size of the current study. The nucleus tractus solitarius is the relay nucleus for dorsal visceral primary afferent fibers in the medulla oblongata, transmitting motor and autonomic signals to the brain after processing internal information [73]. Transcutaneous vagus nerve stimulation (t-VNS) can decrease sympathetic nerve activity through the nucleus tractus solitarius and central nervous system neuron electrical activity, offering a novel approach to PSH treatment [74].

Nonetheless, the mechanism of action requires clarification, and more extensive clinical sample sizes are warranted. Lee et al. determined that stellate ganglion block (SGB) catheterization can improve PSH patient prognosis by overcoming systemic drug therapy limitations and recalibrating abnormal autonomic states [75]. Their pioneering use of SGB in PSH treatment yielded promising results, suggesting SGB as a viable therapeutic option that warrants further clinical investigation.

Recommendations for drug therapy

Regarding the use of pharmacotherapy in patients with PSH, some scholars have provided a general framework: (1) For non-acute PSH episodes, first-line drugs are preferred (propranolol, colistin, etc.), and when the treatment is ineffective, propranolol can be increased to the maximum dosage of the drug or added to the second-line drugs (bromocriptine, etc.) or the third-line drugs (gabapentin, baclofen, etc.), and when it is ineffective again, morphine and other opioids. (2) For acute PSH episodes, diazepam and propranolol may be recommended to control acute episodes [63, 76, 77].

Prognosis

Since PSH is mainly caused by severe craniocerebral injury, which is closely related to the patient's prognosis, there is currently considerable controversy as to whether PSH predicts a poor prognosis for the patient. As early as 1993, some scholars found through a large multi-center study that PSH only reflects the severity of the disease and is not an independent risk factor affecting prognosis. However, subsequent studies conducted at this center achieved utterly different results [78]. Some scholars proposed in 2008 that the emergence of PSH can lead to prolonged hospitalization, increase the risk of delayed complications (weight loss, lung infection, muscle atrophy, etc.), and worsen the prognosis [79]. Clinical academics have pointed out that PSH leads to prolonged hospitalization and poor Glasgow Outcome Scale (GOS). The reason may be that persistent hyperventilation during PSH attacks can cause brain tissue hypoxia; persistent hypertension can lead to aggravation of cerebral edema; persistent tachycardia and hyperhidrosis can lead to cardiac arrest. Functional dysfunction, hypoxia, and cerebral edema can also cause increased intracranial pressure; increased body metabolism can lead to water and electrolyte metabolism disorders, etc., affecting the

patient's prognosis [80]. In 2013, Laxe conducted a 3-year prospective trial of PSH in patients with traumatic brain injury, comparing the prognosis of PSH and non-PSH patients by comparing GOS and disability scores and statistically analyzing the results, which demonstrated that PSH did not affect rehabilitation and post-discharge functional recovery [81].

Conclusion

PSH is a clinical syndrome with complex etiology, whose pathological mechanism has not yet been clarified, with no unified diagnostic standard, which makes it easy to delay the treatment of patients. PSH-AM is the most extensively used clinical diagnostic tool. For patients with suspected PSH, it is recommended to treat their clinical symptoms at an early stage to avoid delays. Currently, the studies on PSH are mostly single-center studies. In the future, we need to consider conducting multi-center large-sample studies with strengthened linkage between clinical and basic research to promote the standardization and precision of PSH treatment and to formulate more clinically appropriate and practical diagnostic standards and treatment protocols.

Author contributions
Peng YinConceptualization, Methodology, Formal analysis, Writing—original draft Yunsong Pan: Conceptualization, Data curation, Writing—original draft Wensheng Dong: Validation, Supervision Deshun Chen: Resources, Software Yongjun Fan: Writing—Review & Editing Jiaqiu Zhu: Data curation Hui Shi: Conceptualization, Supervision, Project administration, Writing—Review & Editing.

Funding
Not applicable.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 18 June 2024 Accepted: 6 April 2025
Published online: 02 May 2025

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