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Paroxysmal Sympathetic Hyperactivity Syndrome (Review)

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Синдром пароксизмальной симпатической гиперактивности (обзор)

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Summary

Paroxysmal sympathetic hyperactivity (PSH) is one of the complications of acute severe brain injuries (traumatic brain injury, intracranial hemorrhage, ischemia, and posthypoxic conditions) in both adults and children. Its high incidence and severe sequelae including organ dysfunction, infectious complications, impaired blood supply to organs and tissues associate with increased disability and mortality. The choice of effective therapy can be challenging because of multifaceted manifestations, diagnostic difficulties, and lack of a clear understanding of the pathophysiology of PSH. Currently, there are various local and international treatment strategies for PSH.

The aim of the review is to summarize clinical and scientific research data on diagnosis and treatment of PSH to aid in the selection of an effective therapy.

Material and methods. Web of Science, Scopus and RSCI databases were employed to select 80 sources containing relevant clinical and research data on the subject of this review.

Results. The key principles of diagnosis and treatment of paroxysmal sympathetic hyperactivity have been reviewed. The current views on etiology and pathogenesis of paroxysmal sympathetic hyperactivity development were outlined. The clinical data concerning complications and sequelae of paroxysmal sympathetic hyperactivity were analyzed. We conclude the review with a discussion of current methods of the syndrome prevention.

Conclusion. Preventing PSH and its adequate and prompt treatment could help avoid the abnormal pathway development following a severe brain injury, reduce its negative consequences and rate of complications, along with the duration of mechanical lung ventilation, patient's stay in ICU, disability and mortality rates. Careful selection of pathogenetic, symptomatic and supportive therapy significantly improves the rehabilitation potential of patients.

Keywords: sympathetic hyperactivity; traumatic brain injury; intracranial hemorrhage; neurovegetative stabilization

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Introduction

The first observation of paroxysmal sympathetic hyperactivity (PSH) published in 1929 was the report of Canadian neurosurgeon Wilder Penfield on the treatment of a 41-year-old woman with cholesteatoma of third ventricle [1]. Later, multiple observations reporting PSH in traumatic brain injury (TBI), intracranial hemorrhage (ICH), ischemic, infectious, posthypoxic, and dysmetabolic brain injuries appeared. Various terms have been used to describe this condition including diencephalic seizures, central autonomic dysregulation, hyperadrenergic state, midbrain syndrome, autonomic dysfunction syndrome, dysautonomia, autonomic storm, sympathetic storm, diencephalic catabolic syndrome (DCS), etc. [2–7]. The study of PSH in the A. L. Polenov Russian Neurosurgical Institute started as early as in the 1950s. The scientists from this institute coined the term «diencephalic catabolic syndrome» and elaborated its pathophysiology, clinical, laboratory and pathological criteria as well as the management strategy [2, 8, 9]. The widely accepted term «paroxysmal sympathetic hyperactivity» was first recommended in 2010 [10, 11].

The International Consensus (2014) developed diagnostic criteria and finally approved the term «paroxysmal sympathetic hyperactivity», which was defined as a syndrome, recognised in a subgroup of survivors of severe acquired brain injury, by simultaneous, paroxysmal transient increases in sympathetic [elevated heart rate, blood pressure, respiratory rate, temperature, sweating] and motor [posturing] activity» [12]. The panel of experts selected 11 of 16 previously considered signs as pathognomonic for PSH. The scales assessing the probability of a PSH diagnosis and its severity were developed (Tables 2 and 3) [12]. Pediatric scales have also been proposed (Table 4) [13].

The aim of this review is to summarize clinical and scientific research data on the diagnosis and treatment of PSH to aid in selecting an effective therapy.

Etiology. Hyperactivity of the sympathetic nervous system may develop following the severe brain injury of any etiology. This illness is probably due to the adaptive «fight or flight» response, universal for mammals and developed during evolution, where the sympathetic nervous system plays the pivotal role. The sympathetic hyperactivity manifestations, initially adaptive, become abnormal after having persisted for a long time.

The risk of PSH is higher in patients with severe TBI (up to 80% of all cases of PSH) [14, 15], intracranial hemorrhages (ICH), hypoxic, dysmetabolic (in particular, hypoglycemic) brain injuries, intracranial hypertension, including those due to hydrocephalus. Less commonly, PSH develops in patients with a brain tumor, acute ischemic cerebrovascular events, meningitis, and encephalitis [16–18]. A review of 349 published cases of PSH showed that about 80% of them developed after TBI, 10% in patients with postanoxic encephalopathy, 5% after cerebrovascular event, while the remaining 5% were associated with hydrocephalus, tumor, hypoglycemia, infections or unspecified causes [10].

The frequency of PSH after traumatic brain injury ranges from 8 to 33% [4, 11, 19]. Retrospective reviews show that PSH most often develops in diffuse axonal damage [20].

The etiology and incidence of PSH in children are comparable to those in adults [21]. The main causes of this syndrome are traumatic brain injury and posthypoxic encephalopathy. Many researchers note that in children the severity of sympathetic hyperactivity is usually higher than in adults, which is associated with age-specific characteristics of the autonomic nervous system [22, 23].

The frequency of PSH decreases over time [10, 24, 25]. A survey of 333 patients in a vegetative state in Italy [25] showed a decrease in the incidence of PSH over time, from 32% (for TBI) and 16% (for other etiologies of vegetative state) between 1998-2005 to 18% and 7% between 2006–2010. There are papers indicating an increase in the incidence of PSH over time [10]. This is mainly due to the increased pain syndrome and autonomic instability caused by discontinuation of opioid analgesics and alpha2-agonists after the patient's transfer from intensive care unit (ICU) to a specialized department or rehabilitation facility. Preparation of the patient for transfer (timely withdrawal of potent drugs, selection of oral medications, adequate nutritional support, and control of infections) allows to reduce the rate of PSH and prevent its increase.

The wide range of reported morbidity makes diagnosing PSH even more difficult. Factors explaining the differences between studies may include variations in design, assessment of underlying disease severity and differential diagnoses, timing, and frequency of PSH evaluation.

Pathogenesis. There are many theories concerning the pathophysiology of paroxysmal sympathetic hyperactivity. None of them is comprehensive. It is still unclear which factors underlie the paroxysms, why they may stop on their own and what affects their frequency and duration.

W. Penfield suggested the epileptogenic theory of PSH origin [1, 26]. In the 1970–80s, the Polenov Neurosurgery Institute considered the syndrome as a nonspecific response of diencephalic structures triggered by brain injury and persisting long after elimination of the damaging factor. This response included impaired consciousness, central hyperthermia, hypothalamic-type respiratory disorders, severe vascular pressure reactions, and widespread neurodystrophy [2, 8]. Particular attention focused

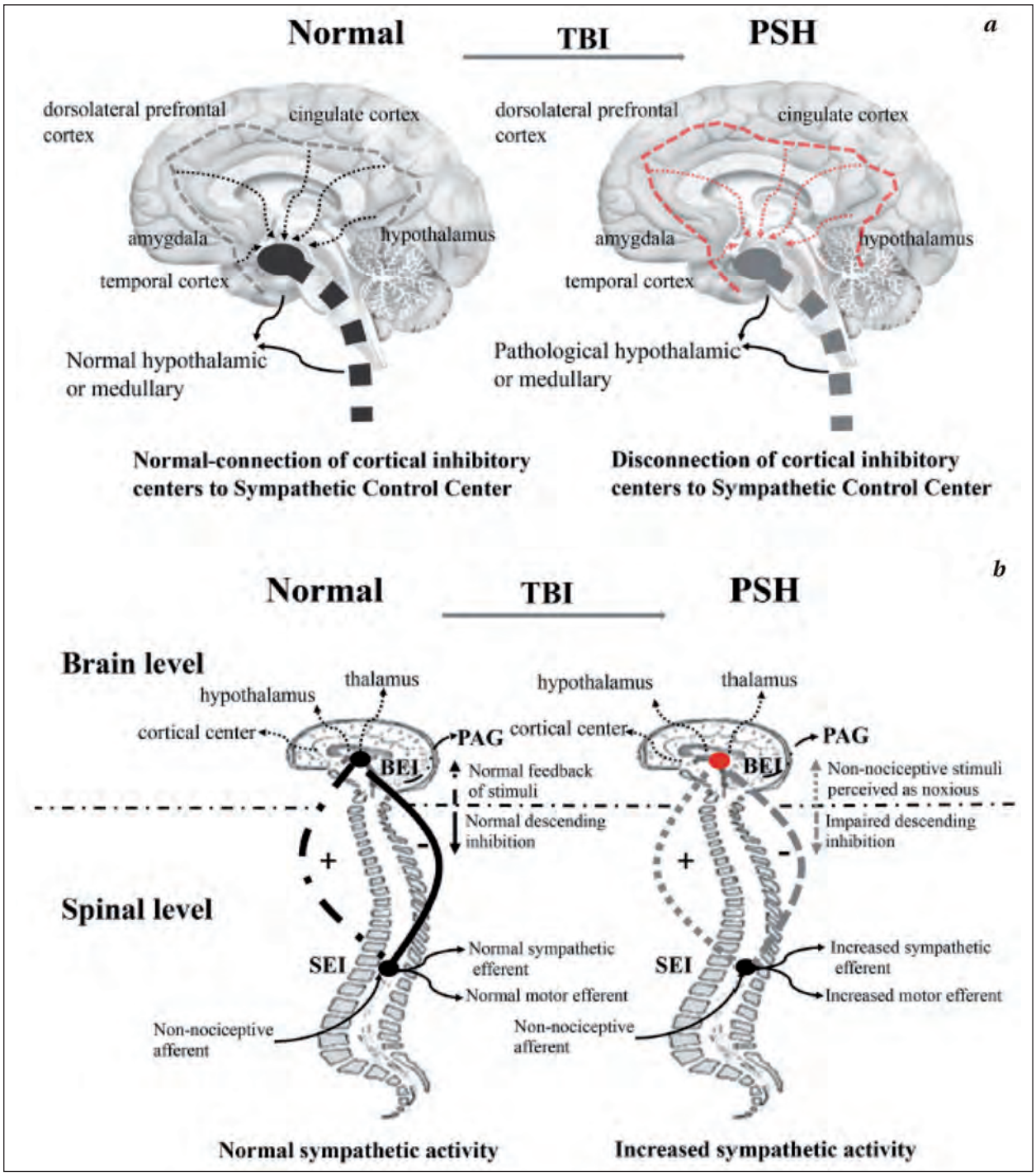

Fig. 1. Disconnection theory and EIR model of the pathogenesis of PSH, by Zheng R-Z, Lei Z-Q, Yang R-Z et al., 2020 [33].
Note. EIR — excitatory/inhibitory ratio; BEI — brain excitatory/inhibitory centers; PAG — periaqueductal gray matter; PSH — paroxysmal sympathetic hyperactivity syndrome; SEI — spinal excitatory/inhibitory centers; TBI — traumatic brain injury.

on changes in the bioelectrical activity of the diencephalic structures, the appearance of delta and theta wave activity [2, 8, 9]. In our opinion, these mechanisms may underlie the pathophysiology of PSH in many cases.

According to one of the current hypotheses, the combination of diffuse and/or focal injury «disconnects» one or several cortical inhibitory centers (such as islet and cingulate cortex) with hypothalamic, diencephalic and brain stem centers responsible for supraspinal control of sympathetic tone (disconnection theory) [27, 28]. The existing disconnection theory (Fig. 1, *a*) is based on the fact that severe paroxysmal activity is associated with impaired regulatory and integrative functions, including those of the brainstem [10, 28]. Sympathetic activity originates in the brainstem, hypothalamus, and spinal cord. The anterior hypothalamus and medulla ob-

longata are considered to be the main regions involved in central sympathetic nervous system activation [20, 28, 29]. Sympathetic activity inhibition occurs in cortical structures such as hippocampus, amygdala, insular, cingulate, medial temporal, and dorsolateral prefrontal cortex [30]. Subsequently, a more detailed study showed that disconnection of one or more brain centers or cortical and subcortical abnormalities caused by focal lesions or diffuse injuries lead to autonomic dysfunction [28]. Despite the existing evidence supporting the theory of disconnection of cerebral inhibitory pathways from excitatory centers, it is still insufficient to explain all the symptoms observed in patients with PSH.

Normally, various cortical, hypothalamic, thalamic, and other subcortical areas modulate activity in brainstem centers with the periaqueductal gray matter considered a key center that inhibits excitation [30]. The periaqueductal gray matter has an inhibitory effect on spinal reflex arcs, thus maintaining the balance between inhibitory and excitatory inter-neuronal influences on motor and sympathetic efferents and allowing adequate perception of normal sensory stimuli as non-threatening. In the excitatory/inhibitory ratio model (EIR), disabling the descending inhibition causes maladaptive dendritic arborization and spinal circuit excitation, and even minor stimuli (temperature change, tactile stimulation, and others) can be perceived as strong and cause increased motor and sympathetic activity [27, 28]. This is complicated by a relative decrease in functional dopaminergic activity. As a result, activation of the sympathetic nervous system and increased levels of circulating catecholamines develop [27] (Fig. 1, *b*). The presented model describes PSH as a two-stage pathological process. First, excitation occurs due to the disabling of descending inhibitory pathways, and second, the paroxysm stops when inhibitory factors are restored [10, 27, 28, 31]. This theory explains the abnormally enhanced and prolonged response to stimuli that are either not nociceptive or are only minimally nociceptive (e. g., tracheal lavage) as an allodynamic adaptation, resembling the phenomena observed in chronic pain syndromes. The paroxysm triggers include vascular spasm and increased intracranial pressure with a reported case of paroxysm development after abrupt termination of hypothermia procedure [32]. The proposed theory explains why patients with lesser injury of the brain stem have shorter duration of paroxysms and much faster onset of inhibition in the upper parts of the spinal cord. It also suggests that paroxysmal sympathetic symptoms may be a response to structural or functional disturbances of the midbrain in patients with TBI [10].

Figure 1, *a* presents the disconnection theory. On the left, normal connection of the cortical inhibitory center (islet and cingulate cortex) with the sympathetic centers (hypothalamic, diencephalic, and stem) is shown. On the right, disconnection of the cortical inhibitory centers from the sympathetic center during TBI is depicted.

A part of Figure 1, *b* presents the model of impaired excitation-inhibition relationship. On the left, normal variant is shown as cortical and subcortical, hypothalamic and thalamic centers modulate activity of incoming signals and then exert inhibitory effect on the spinal reflex activity. At the spinal cord level, spinal centers normally provide afferent feedback (afferent) from sensory receptors perceiving various stimuli (pain, temperature, tactile etc.) and exert efferent action (sympathetic and motor). On the right, disabling descending inhibition leads to excitation of the feedback loop, with a minor stimulus potentially perceived as a strong one.

It has been suggested that an imbalance between the sympathetic and parasympathetic nervous system underlies PSH [27, 28, 33].

Neuroinflammation is considered to be one of the causes of PSH. Elevated levels of interleukins stimulate the sympathetic activity [34]. In severe brain injury, neuroinflammation can become chronic and trigger sympathetic overactivity.

Recently, increasing attention has been paid to disorders of neuroendocrine regulation [35]. In the neurotransmitter system, paroxysms occur due to uncontrolled activity of the adrenergic system, leading to increased circulation of catecholamines [10, 33, 36, 37]. Studies show that the blood levels of adrenocorticotropic hormone, adrenaline, noradrenaline, and dopamine significantly increase during paroxysms, while the levels of noradrenaline and dopamine decrease during the interictal period [19, 33, 36].

Although the anatomy of PSH pathogenesis is still uncertain, several studies have shown that focal brain parenchymal lesions increase its likelihood [33, 38]. A more detailed characterization of structural lesions has been obtained using neuroimaging techniques [33]. Patients with deeper brain lesions in the periventricular white matter, the corpus callosum or stem were more likely to develop PSH than those with lesions in the cortex and subcortical structures [33, 39].

Symptoms. PSH is characterized by impaired consciousness (depression or agitation), hyperhidrosis, fever, increased heart rate, respiratory rate, hypertension, mydriasis, increased muscle tone, dystonia, hyperkinesis and myoclonus [10, 33, 40, 41] (Table 1).

Sympathetic crises can develop from 1 to 15 times per day and last from 10 to 30–40 minutes [4]. Symptoms are thought to persist for several months to several years, with one study showing a mean duration of 5 years after trauma [4].

Table 1. The symptoms of PSH.

Organs and systems	The symptoms
Cardiovascular system	Tachycardia
	Increased myocardial contractility
	Increased cardiac output
	Hypertension
Bronchopulmonary system	Tachypnea
	Bronchial dilation
	Pulmonary edema
Eyes	Pupillary dilation
Gastrointestinal tract	Decreased motility
	Malabsorption
	Ileus
Musculoskeletal system	Muscle tone increase
	Dystonia
	Contractures
	Spasticity
	Myoclonus
Skin	Increased redness
	Sweating

Table 2. Diagnostic criteria of PSH (Clinical Feature Scale, CFS)

Criteria	Points			
	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 (°C)	<37,0	37,0–37,9	38,0–38,9	⩾39
Sweating	Absent	+	++	+++
Posturing during episodes	Absent	+	++	+++

Table 3. Additional criteria for PSH (Diagnosis Likelihood Tool, DLT).

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

Table 4. Pediatric score for the diagnosis of PSH.

Parameter	Points							
	0		1		2		3	
Years	1–4	5–15	1–4	5–15	1–4	5–15	1–4	5–15
Heart rate (per min)	<110	<100	110–124	100–119	125–139	120–139	⩾140	
Respiratory rate (per min)	<30	<25	30–34	25–29	35–39	30–34	⩾40	⩾35
Systolic blood pressure (mmHg)	<100	<120	100–109	120–129	110–119	130–139	⩾120	⩾140
Diastolic blood pressure (mmHg)	<65	<75	65–72	75–82	73–79	83–89	⩾80	⩾90
Temperature, °C	<37		37–37,9		38–38,9		⩾39	
Sweating	Normal		Increased		Localized diaphoresis		Generalized diaphoresis	
Muscle tone increase	Absent		Mild increase		Neat increase		Generalized spasticity or opisthotonus	

Diagnosis. Diagnostic criteria for PSH were defined by an international consensus in 2014 (Tables 2, 3) [12]. In the same year, diagnostic scales for children were proposed [13] (Table 4).

Additional criteria (Diagnosis Likelihood Tool) were defined for the confirmation of the diagnosis (Table 3).

Based on the total score of CFS and DLT, a decision on the diagnosis of PSH is made: unlikely < 8 points, possible 8–16 points, probable > 17 points.

The researchers at Polenov Neurosurgical Institute developed original criteria for the diagnosis of PSH in 2019 [3, 42] (Tables 5, 6).

Table 5. Diagnostic criteria for PSH.

Parameter	Points			
	0	1	2	3
Main criteria				
Heart rate (per min)	< 100	100–119	120–139	⩾140
Systolic blood pressure (mmHg)	< 140	140–159	160–179	⩾180
Respiratory rate (per min)	< 18	18–23	24–29	⩾30
Kerdö Autonomic Index	0	+1–+10	+11–+20	>+21
Body temperature, °C	< 37,0	37,0–37,9	38,0–38,9	⩾39,0
Muscle tone increase (Ashworth Scale)	0	1–2	3	4–5
Sympathetic over-reactivity (24 h)	Absent	1–3	4–6	>6
Additional criteria				
Glasgow coma scale	15	14–13	12–10	<10
Sweating	Absent	+	++	+++
Skin redness	Absent	+	++	+++
Albumin (g/l)	34–48	28–33	22–27	<22
EEG signs of diencephalic abnormalities	Absent	+	++	+++

Table 6. Differential diagnostic criteria.

Parameters	Points		
	1	2	3
Difference in body temperature, °C	0,5–0,6	0,7–0,9	⩾1
Serum procalcitonin (ng/ml)	>0,5	>2	>10
The presence of pain syndrome	+	++	+++
Heart rate (per min)	80–99	60–79	<60
Systolic blood pressure (mmHg)	90–100	80–89	<80
Body temperature, °C	<36,0	<35,5	<35,0

Score interpretation Table 5:

0 — condition absent

1–7 points (main criteria) and not more than 5 points (additional criteria) — mild PSH

8–14 points (main criteria) and not more than 10 points (additional criteria) — moderate PSH

15–21 points (main criteria) and 10–15 points (additional criteria) — severe PSH

Score interpretation Table 6:

1–5 points — likely association with other conditions requiring additional diagnosis and treatment

5–11 points — PSH is questionable or does not play a major role

11–18 points — PSH is ruled out

Extras:

- Assessment is done only with normovolemia, pO_2>60 mmHg or SpO_2>90%, pCO_2<45 mmHg, and blood glucose >3.5 mmol/l.
- Difference in body temperature implies that between the rectal and axillary values
- Kerdö Autonomic Index = 100×(1-DBP/HR) (DBP — diastolic blood pressure, HR — heart rate)
- + mild
- ++ moderate
- +++ severe
- The level of consciousness is assessed using the Glasgow Coma Scale
- The muscle tone is assessed using the Ashworth Scale.
- Assessment of pain syndrome in conscious patients can be made using a 5-point verbal pain rating scale (Frank A. J. et al., 1982) [50], where 1 point equals +; 2–3 points, ++, and 4 points, +++.
- The level of sympathetic overactivity is assessed at least once a day
- The use of differential diagnostic criteria in the initial and each subsequent evaluation is mandatory.

Some researchers believe that PSH develops in a stepwise manner [33]. The first stage is often asymptomatic because the patient in the early acute phase of brain injury receives various sedatives, narcotic analgesics and myorelaxants. The second stage is characterized by tachycardia, hypertension, tachypnoea, hyperhidrosis, while the third one manifests with muscle tone disorders and dystonia [4].

The diagnosis of PSH is based on clinical signs and symptoms being largely a diagnosis of exclusion. The differential diagnostic list includes sepsis, hypoxemia, hypercapnia, hypoglycemia, seizures, pulmonary embolism, thyrotoxic crisis, acute myocardial infarction, alcohol or drug withdrawal, malignant neuroleptic syndrome, serotonergic syndrome, malignant hyperthermia, and intracranial hypertension [3, 4, 33, 43, 44].

Complications of PSH. Numerous studies have shown that PSH associates with unfavorable long-term outcomes such as impaired consciousness, late recovery of consciousness, impaired motor functions, multiple organ failure, malnutrition, infectious complications, prolonged mechanical ventilation, longer ICU stay, low scores on Glasgow Outcome Scale, increased disability and mortality (Table 7) [3, 4, 33, 45, 46]. Patients with prolonged unconsciousness and PSH have less rehabilitation potential than those with stable autonomic status [25, 33, 46, 47].

Meanwhile, several studies have shown that PSH is not associated with serious complications and has no effect on the outcome [4, 21].

Table 7. Complications of PSH.

Organs and Systems	Complications
Nervous system	Decrease in the level of consciousness
	Abnormal circadian rhythms
	Excitation
	Convulsions
Skin and mucous membranes	Trophic disorders
	Sweating
	Skin redness
	Increased skin grease
Musculoskeletal system	Polyneuropathy
	Polymyopathy
	Muscular dystrophy
	Spasticity
	Dystonia
	Myoclonus
	Contractures
Cardiovascular system	Arterial hypertension
	Myocardial infarction
	Acute coronary syndrome
	Arrhythmias
	Myocardial dystrophy
Bronchopulmonary system	Bronchorrhea
	Pulmonary edema
Gastrointestinal tract	Motility disorders (nausea, vomiting, constipation, diarrhea)
	Malabsorption
	Erosions and ulceration of the mucous membrane
Endocrine system	Increased activity of the hypothalamic-pituitary-adrenal and the renin-angiotensin-aldosterone systems
	Hypogonadism
	Temperature regulation disorders
Immune system	Decreased immunity, chronic infections
Other organs	Neurogenic dystrophy
	Multiple organ dysfunction

Such discrepancies in the results of studies can be related both to their design and methodology. The choice of the control group is essential because the severity of brain injury in this group should be comparable with that of the main group. The occurrence and severity of PSH sequelae largely depend on its severity and duration. Based on our own observations and literature data, we can argue that the PSH significantly aggravates the underlying disease and its outcome, reducing the rehabilitation potential [3, 4, 46–48].

Prevention. Prevention of PSH in critically ill patients can significantly decrease the rate of complications, increase survival rate and reduce the duration of ICU stay [3, 33].

International researchers report that currently there are no effective measures for PSH prevention [4, 10, 33]. There are several drugs recommended to reduce the frequency of paroxysms, which are commonly referred to as prophylactic. These include clonazepam, bromocriptine, propranololol, oxycodone, gabapentin, clonidine, baclofen. Clinical experience shows that prolonged sympathetic overactivity is less susceptible to correction [3, 43, 49]. In our opinion, the therapeutic anesthesia technique according to Professor Kondratyev (described in detail in the next section) and therapeutic hypothermia, in particular craniocerebral hypothermia (CCH), could be considered preventive for PSH.

Treatment. PSH therapy methods is usually classified into non-pharmacological, pharmacological, and prophylactic ones. The treatment of PSH should be primarily based on general ICU principles (adequate correction of hemodynamics, gas exchange, fluid volume, nutritional support, electrolyte balance, blood glucose level, and body temperature) [3, 4, 10, 33, 49–51]. Prior to treatment, the identification of leading signs and symptoms requiring therapy is mandatory [2, 33]. Careful daily calculation of volumetric balance with consideration of abnormal fluid and electrolyte loss through respiration, sweat, vomiting or diarrhea is also essential. Thus, in patients with hyperhidrosis, fluid replacement is sometimes sufficient to increase the level of consciousness and reduce the frequency of paroxysms [10, 33].

Nutritional support with calculation of caloric intake, basic nutrient and mineral requirements, has a pivotal role. Energy expenditure during a paroxysm increases threefold compared to the interictal period [33, 53]. In addition, problems with digestion of administered food are common in PSH, which is due to both sympathetic overactivity effect on gastrointestinal functions and prolonged antibiotic therapy. Therefore, it is often necessary to prescribe enzyme preparations, pre- and probiotics. Adequate selection of an optimal caloric intake, nutritional volume, and types of nutritional support can reduce the frequency and severity of paroxysms,

as well as their negative sequelae [33, 53]. Maintenance of normal body weight is one of the priority tasks.

Proper care, including maintaining a comfortable temperature and humidity, preventing bedsores pain, and contractures, is another important aspect [4, 33, 54].

Hyperbaric oxygenation could be another nonpharmacological treatment method to increase oxygen availability and improve aerobic metabolism in damaged tissues [33].

Physical therapy and therapeutic exercise can reduce the severity of spasticity, prevent contractures, muscular dystrophy, trophic skin disorders, and pain syndrome and increase their treatment efficacy [10].

The choice of drug therapy depends on the severity of the underlying disease, a comprehensive analysis of clinical manifestations and the individual characteristics of the patient [10, 54, 55]. Thus, in the acute phase of the disease parenteral medications are preferable, while at the time of patient transfer from ICU and the start of rehabilitation oral therapy could be more efficient. Transcutaneous drug delivery (patches) is increasingly common and convenient to use [33].

According to international authors, drug treatment usually begins with symptomatic therapy including β-blockers, gabapentin, benzodiazepines, valproate [10, 19, 33, 54–61]. When the treatment is not effective, continuous administration of opioids and propofol is suggested. During last 10–15 years after dexmedetomidine was introduced in practice, alpha2-agonists have been successfully used for PSH [33, 62, 63, 65–70]. The issue of duration of administration of opioids, hypnotics, and alpha2-agonists is still unresolved. Premature drug discontinuation can lead to recurrence of PSH, however their prolonged use could delay rehabilitation and result in multiple side effects. Using the «diagnostic window» approach, reducing the number of drugs administered and a smooth transition to oral drug ingestion allows to avoid many treatment complications [3, 50].

The use of neuroleptic drugs should be avoided because of the risk of malignant neuroleptic syndrome [3, 4, 50, 51].

Interestingly, some differences exist in the action of the same drugs depending on the etiology of brain injury, in particular, traumatic and nontraumatic. Thus, fentanyl and propofol effectively reduce blood pressure and heart rate in traumatic PSH, whereas they are not effective in nontraumatic lesions [64]. This is probably due to the polymorphic character of brain damage in TBI.

In clinical practice, most patients require treatment with multiple potentially synergistic drugs useful for both for symptomatic treatment and paroxysm prevention [3, 10, 33, 54, 55, 64].

Our long-term observations have shown that the therapeutic anesthesia developed in the 1990s by Professor A. N. Kondratyev can be considered as a pathogenetic therapy for PSH [3, 43, 50, 51, 71].

The main objectives of therapeutic anesthesia include creation of neurovegetative stability, a comprehensive protective reaction in response to brain damage, and ensuring an adequate functional level without abnormal components, which is sufficient for maintenance of compensatory reactions and integrative activity necessary for recovery [43, 50]. Anesthesia technique includes intravenous continuous injection of the opioid analgesic fentanyl 0.5–1 μg/kg/h, an alpha2-agonist (such as clonidine 0.2–0.7 μg/kg/h or dexmedetomidine 0.2–0.5 μg/kg/h), propofol 2–5 mg/kg/h (not longer than 24 hours due to a risk of «propofol infusion syndrome»), and sodium thiopental 2–4 mg/kg/h. Duration of therapy ranges from 12 hours to 7–10 days [3, 43, 50, 51].

Hypothermia sessions are an obligatory component of acute severe brain injury therapy and prevention of PSH [3, 42]. Severe brain injury causes focal hyperthermia caused by neuronal excitation, glutamate and aspartate release, activation of free radical reactions and neuroinflammation. The difference between the temperatures of individual brain regions can reach 2–4°C [72]. A decrease in neuronal temperature results in reduced metabolism and decreased oxygen and glucose requirements of brain cells. Hypothermia helps to reduce neuroinflammation and limit ROS formation and pro-apoptotic reactions [73–76]. Craniocerebral hypothermia (CCH) is one of the effective cooling methods. The technique consists in lowering the scalp temperature to 5–8°C using helmets with circulating fluid, maintaining the skin temperature at a constant level during the entire session. The duration of cooling ranges from 12 hours to 7 days, if the temperature rises after the cooling cessation, the procedure is repeated until stable normothermia is achieved. Smooth withdrawal from a hypothermia session is crucial [3, 42, 75, 76]. Abrupt withdrawal, as mentioned above, can become a trigger for new paroxysms of PSH.

Once the symptoms and signs of PSH appear after the withdrawal of therapeutic anesthesia, continuous intravenous clonidine or dexmedetomidine, β-blockers, antiepileptic drugs (phenytoin, clonazepam), nonsteroidal anti-inflammatory drugs and other symptomatic agents are commonly used [3, 42].

In the Polenov Russian Neurosurgical Institute, the management strategy is based on the assessment according to original scales (Tables 5, 6) (Fig. 2).

The duration of therapy is individual. The patient is regularly assessed using the «diagnostic window» approach [3, 42].

Despite the considerable interest of experts in the study of PSH, many aspects remain unclear.

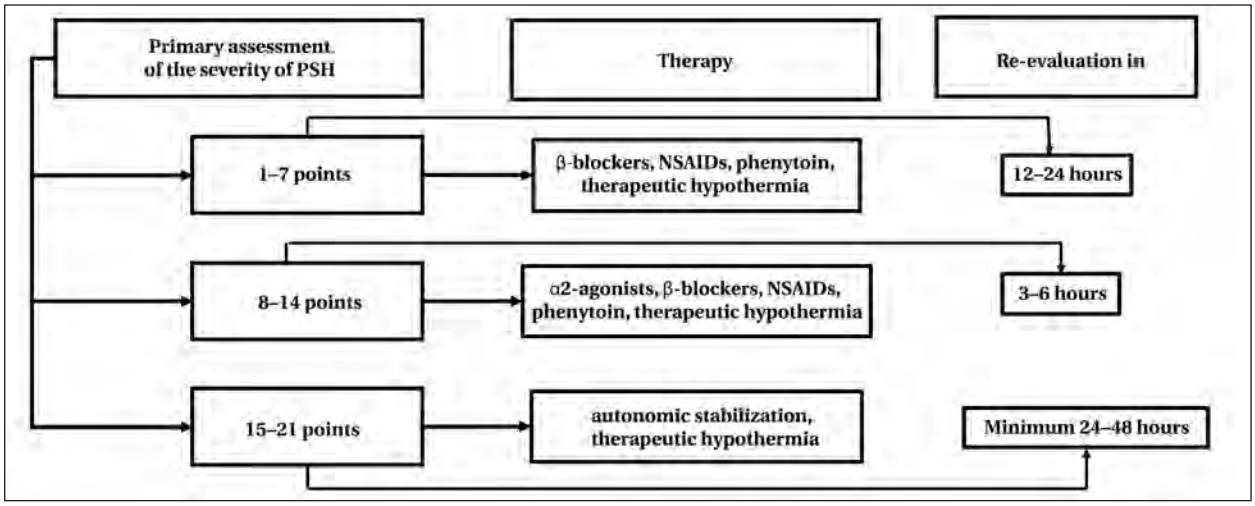

Fig. 2. Algorithm of management of PSH.
Note. NSAIDs — non-steroidal anti-inflammatory drugs.

They include triggering and maintaining mechanisms, optimal diagnostic criteria, efficient differential diagnosis strategy, severity assessment, as well as the most appropriate preventive and therapeutic modalities [10, 33, 77–79]. Although severe brain injury is frequently complicated by PSH, it is still difficult to aggregate and manage all the available data due to the lack of generally accepted diagnostic and treatment strategies [10, 33, 79, 80].

Conclusion

Prevention of PSH and its adequate and timely treatment could preclude the pathological pathway development in severe brain injury, allowing to reduce the negative sequelae and associated complications, as well as the duration of mechanical ventilation, patient's stay in ICU, morbidity, and mortality. The selection of pathogenetic, symptomatic and supportive therapy significantly improves the rehabilitation potential of patients. In addition to drug treatment, ensuring comfortable environment (temperature, humidity, protection from harsh sounds, strong smells, and other stimuli), proper care and nutritional support is equally important for patients with PSH. Rehabilitation measures conducted in patients with autonomic instability are both ineffective and harmful since they can provoke PSH paroxysms and increase their frequency.

Further study of this challenging syndrome will help intensivists, neurologists, and rehabilitation specialists to timely provide symptomatic and pathogenetic therapy.

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