Paroxysmal Sympathetic Hyperactivity（PSH）：発作性交感神経過活動

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【概念】

PSHは、重篤な脳損傷に引き続き、発作性に高熱、高血圧、頻脈、頻呼吸、発汗、筋緊張の異常など過度の自律神経緊張症状を呈する状態で、通常は発作性交感神経興奮状態を呈する。

【症状】

典型的には、心拍数上昇、血圧上昇、呼吸数上昇、発汗、体温上昇、筋硬直などの症状が発作性に1日に5回程度生じ、1回生じると約30分継続する。PSHは合併症として高熱、脱水、筋肉量減少、筋拘縮を起こし、転帰に重篤な影響を与える。これらの合併症は早期診断して治療することで回避できるが、PSHの概念自体を知らないと対応ができない。

【名称について】

本病態は、dysautonomia、paroxysmal autonomic instability with dystonia、paroxysmal sympathetic storm、sympathetic storm、autonomic storm、diencephalic seizure、autonomic dysfunction syndromeなどの名称で報告されていた。現在では「交感神経系が発作性に興奮状態になる病態」を適切に表現したPSHが妥当とされる 。

◯発生機序

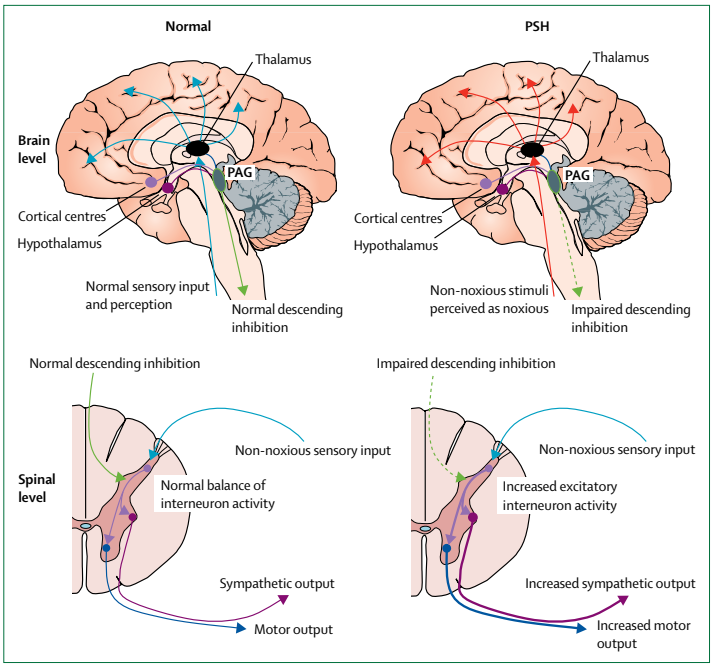

Figure 2: **Excitatory:inhibitory ratio model of the pathogenesis of PSH**
In normal circumstances, various cortical, hypothalamic, thalamic, and other subcortical inputs modulate activity within brainstem centres—the PAG is shown here as one of the key brainstem hubs in this process. These brainstem nuclei provide inhibitory drive to spinal-reflex arcs, thereby maintaining balance between inhibitory and excitatory interneuron influences on motor and sympathetic efferents, allowing normal sensory stimuli to be perceived as non-noxious. In the excitatory:inhibitory ratio 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).[35,36] PAG=periaqueductal grey. PSH=paroxysmal sympathetic hyperactivity.

脳波上てんかん波が認められず、抗てんかん薬が無効であったことから、てんかん原性は否定されている。視床下部や脳幹の交感神経興奮中枢が、より高位の大脳皮質などのコントロールから離れ、結果として交感神経興奮状態になっている、あるいは、脊髄における求心性刺激処理をコントロールする間脳・脳幹が傷害され抑制がきかなくなり、脊髄に入る求心路から過剰反応が生じる機序が考えられ、後者が有力である。

【疫学】
病名が一定せず、診断基準もなかったので、頻度に関しては混乱がある。若年者に多い。Hughesらの報告では、患者年齢は平均33.6歳である。本邦での報告は非常に少ない。この理由は不明であるが、病態に対する注目や理解が乏しく、報告されていない可能性もある。

【原因となる脳疾患・脳損傷】
PSH報告例の約80%が頭部外傷後で、2番目に多いのは低酸素(9.7%)である。脳虚血、低酸素性脳症や脳卒中が原因になることもある。Baguleyらは重症頭部外傷後のPSH患者の解析で、患者の63%は病院への搬送前に低酸素状態であったと報告しており、低酸素がPSHの原因として過小評価されていることが示唆される 。くも膜下出血もPSHの原因とされており、交感神経過緊張状態となることから、PSHと遅発性脳血管攣縮との関係も示唆される。

【診断】
2007年にRabinsteinが、以下の1〜6のうち少なくとも4つの症状を発作的に呈するものをPSH とする基準を示した。

①発熱：2日間連続して少なくとも1日1回は＞38.3 ℃のエピソード
②頻脈：脈拍数＞120/min(β遮断薬服用時は＞100 /min)
③高血圧：収縮期血圧＞160mmHg(β遮断薬服用時は＞140 mmHg)
④頻呼吸：呼吸数＞30/min
⑤過度の発汗
⑥伸展姿勢もしくは高度の筋緊張異常

以上に加えて、頻度は低いが、不穏状態、鳥肌、瞳孔散大、歯ぎしりも特徴である。診断基準を厳密にすることも必要かもしれないが、むしろ緩くして早期 診断・治療につなげることが臨床上重要である。
また、mixed autonomic hyperactivityと称する、低血圧、徐脈、徐呼吸など、副交感神経症状を伴う症例も存在する。

総説を含めPSHを多数報告しているBaguleyを中心とした国際コンセンサス会議で疾患概念の整理と新たな診断基準が提唱され、そこでは他病態との鑑別を目的としたdiagnosis likelihood toolと、症例によって各交感神経症状の強度が異なることを考慮したclinical feature scaleの2項目それぞれをスコア化し合計した29点満点中17点以上でprobable、8-16点でpossibleとしている（Baguley IJ et al. J Neurotrauma. 2014; 31: 1515-1520）。

Meyfroidtらは頭部外傷後に生じる交感神経系”storm”としてのPSHについて、その疾患概念や病態、診断のためのスコアリング、推奨される治療薬についてまとめている。（Meyfroidt G et al. Lancet Neurol 2017; 16: 721-729）。

Table 1. Paroxysmal Sympathetic Hyperactivity—Assessment Measure

Clinical Feature Scale (CFS)

	0	1	2	3	Score
Heart rate	<100	100–119	120–139	≥140	
Respiratory rate	<18	18–23	24–29	≥30	
Systolic blood pressure	<140	140–159	160–179	≥180	
Temperature	<37	37–37.9	38–38.9	≥39.0	
Sweating	Nil	Mild	Moderate	Severe	
Posturing during episodes	Nil	Mild	Moderate	Severe	
			CFS subtotal		

Severity of clinical features	Nil	0	
	Mild	1–6	
	Moderate	7–12	
	Severe	≥13	

Diagnosis Likelihood Tool (DLT)

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	
(Score 1 point for each feature present) DLT subtotal	

Combined total (CFS + DLT)	

PSH diagnostic likelihood	Unlikely	<8	
	Possible	8–16	
	Probable	>17	

PSH, paroxysmal sympathetic hyperactivity.

A Clinical feature scale (CFS) score

	0	1	2	3
Heart rate (beats per min)	<100	100–119	120–139	≥140
Respiratory rate (breaths per min)	<18	18–23	24–29	≥30
Systolic blood pressure (mm Hg)	<140	140–159	160–179	≥180
Temperature (°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 (DLT): one point per feature present

Antecedent acquired brain injury
Clinical features occur simultaneously
Episodes are paroxysmal in nature
Sympathetic over-reactivity to normally non-noxious stimuli
Absence of parasympathetic features during episodes
Features persist for >3 consecutive days
Features persist for >2 weeks post-brain injury
Two or more 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

- **CFS subtotal=**
  sum of CFS scores for each of the six features (0–3 points for individual features; maximum subtotal=18);
  CFS 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 score:
  <8=PSH unlikely; 8–16=PSH possible; ≥17=PSH probable

Figure 1: **The PSH Assessment Measure**
The PSH Assessment Measure (PSH-AM; appendix) is calculated using two constructs: (A) the clinical feature scale (CFS), which measures the intensity of the cardinal features identified as crucial to PSH; and (B) the diagnosis likelihood tool (DLT), which is based on the presence of contextual attributes (identified by expert consensus), and indicates the likelihood that the observed features are due to PSH. (C) The PSH-AM score is calculated by combining the CFS and DLT subtotal scores, which gives an estimate of the probability of a diagnosis of PSH. Adapted from Baguley and colleagues,[15] by permission of Mary Ann Liebert, Inc. PSH=paroxysmal sympathetic hyperactivity.

【治療】

PSHを生じた重症頭部外傷症例に対しては全身管理が重要であり、二次的脳損傷予防のため発熱は積極的に管理すべきである。岡田らの報告においても、PSH期間中、体温上昇や血圧上昇によって二次的脳損傷を増悪させるリスク、発汗過多によって脱水、腎前性腎不全、深部静脈血栓症が生じるリスクなどを是正するため、長期間の人工呼吸下の集中治療を行っている。

PSH自体の抑制に最初に用いるべき治療薬としては、モルヒネ、ベンゾジアゼピン系薬物、β遮断薬、バクロフェン〔γ-aminobutyric acid(GABA)-B受容体アゴニスト〕、ガバペンチン(GABA誘導体)、クロニジン(α2受容体アゴニスト)が知られている。それらの薬剤で治療効果が不十分であれば、ブロモクリプチン(ドパミンアゴニスト)も併用されることがある。β遮断薬は頻用されるが、効果の評価は不十分である。特にガバペンチンの有効性を報告する論文が増えており、西田らは重症頭部外傷後第11病日から生じたPSHに対してガバペンチン投与が有効であったが、投与中止で再燃したとしている。岡田らの報告でも、2症例でガバペンチンが有効であった。ガバペンチンは求心性神経刺激を抑制性に調節することによって有効性を示すと考えられている。また、ガバペンチンとβ遮断薬の併用も試みられている。難治例ではバクロフェン髄注療法が行われることがあるが、バクロフェンの胃内投与は無効である。抗てんかん薬は一般に無効である。

	Prevention or treatment: dose and route*	Site of action	Clinical features targeted	Evidence of efficacy†	Cautionary notes
Opioids					
Morphine‡[40]	Prevention: intravenous infusion, titrate to effect Treatment: 1–10 mg intravenous bolus	Opioid receptors in brain and spinal cord (and possibly in peripheral tissue)	Most features, particularly hypertension, allodynia, and tachycardia	Consistent	Respiratory depression, tolerance, and need for dose escalation
Fentanyl[41]	Prevention: patch 12–100 μg/h	Opioid receptors in brain and spinal cord (and possibly in peripheral tissue)	Most features, particularly hypertension, allodynia, and tachycardia	Consistent	Respiratory depression, tolerance, and need for dose escalation
Intravenous anaesthetics					
Propofol	Prevention: intravenous infusion; maximum <4 mg/kg per h Treatment: 10–20 mg intravenous bolus	$GABA_A$ receptors in brain	Most features	Consistent	Only if mechanically ventilated, and in acute phase
β-adrenergic blockers					
Propranolol[42–44]	Prevention: 20–60 mg every 4–6 h, orally (rectal administration also described)	Non-selective β adrenoceptors (central, cardiac, and peripheral)	Tachycardia, hypertension, and diaphoresis; might help with dystonia	Consistent	Bradycardia, hypotension, bradyarrhythmia, sleep disturbances, and masked hypoglycaemia, especially with oral antidiabetics
Labetalol[45]	Prevention: 100–200 mg every 12 h, orally	β and α adrenoceptors	Tachycardia, hypertension, and diaphoresis; might help with dystonia	Limited	Bradycardia, hypotension, bradyarrhythmia, sleep disturbances, and masked hypoglycaemia, especially with oral antidiabetics
Metoprolol	Prevention: 25 mg every 8 h, orally	Cardioselective β adrenoceptors	Limited or no impact on any features	Ineffective	Bradycardia, hypotension, bradyarrhythmia, sleep disturbances, and masked hypoglycaemia, especially with oral antidiabetics
α2 agonists					
Clonidine[46]	Prevention: 100 μg every 8–12 h, orally; titrate to a maximum of 1200 μg/day Prevention: intravenous infusion; titrate to effect	α2 adrenoceptors in brain and spinal cord	Hypertension and tachycardia	Intermediate	Hypotension, bradycardia, and sedation; intravenous infusions are not a long-term solution
Dexmedetomidine[47,48]	Prevention: intravenous infusion; titrate to effect Prevention and treatment: 0·2–0·7 μg/kg per h	α2 adrenoceptors in brain and spinal cord	Hypertension and tachycardia	Intermediate	Hypotension, bradycardia, and sedation; intravenous infusions are not a long-term solution
Neuromodulators					
Bromocriptine[34,46]	Prevention: 1·25 mg every 12 h, orally; titrate to a maximum of 40 mg/day	Dopamine D_2 receptors	Temperature and sweating	Intermediate	Confusion, agitation, dyskinesia, nausea, and hypotension
Gabapentin[49]	Prevention: 100 mg every 8 h, orally; titrate to a maximum of 4800 mg/day	α2δ presynaptic voltage-gated Ca^{2+} channels in brain and spinal cord	Spasticity and allodynic responses	Consistent	Well tolerated
Baclofen[50–52]	Prevention: 5 mg every 8 h, orally; titrate to a maximum of 80 mg/day Prevention: intrathecal—specialist use only	$GABA_B$ receptors	Spasticity and dystonia	Orally: limited; intrathecal: consistent	Sedation and withdrawal syndrome

(Table 2 continues on next page)

	Prevention or treatment: dose and route*	Site of action	Clinical features targeted	Evidence of efficacy†	Cautionary notes
(Continued from previous page)					
Benzodiazepines					
Diazepam	Treatment: 1–10 mg intravenous bolus	Central benzodiazepine receptors on GABA complexes in brain and spinal cord	Agitation, hypertension, tachycardia, and posturing	Intermediate	Sedation; use intravenous boluses with caution in patients without secure artificial airway
Lorazepam	Treatment: 1–4 mg intravenous bolus	Central benzodiazepine receptors on GABA complexes in brain and spinal cord	Agitation, hypertension, tachycardia, and posturing	Intermediate	Sedation; use intravenous boluses with caution in patients without secure artificial airway
Midazolam	Treatment: 1–2 mg intravenous bolus	Central benzodiazepine receptors on GABA complexes in brain and spinal cord	Agitation, hypertension, tachycardia, and posturing	Intermediate	Sedation; use intravenous boluses with caution in patients without secure artificial airway
Clonazepam	Prevention: 0·5–8·0 mg/day, orally in divided doses	Central benzodiazepine receptors on GABA complexes in brain and spinal cord	Agitation, hypertension, tachycardia, and posturing	Intermediate	Sedation; use intravenous boluses with caution in patients without secure artificial airway
Sarcolemmal Ca^{2+} release blockers					
Dantrolene[46]	Treatment: 0·5–2 mg/kg intravenous every 6–12 h; titrate to a maximum of 10 mg/kg per day	Ryanodine receptors in cell membranes of striated muscle fibre cells	Posturing and muscular spasms	Intermediate	Hepatotoxicity and respiratory depression

These data are provided as a record of published reports of drugs used to treat patients with PSH, and not as recommendations for treatment. Drug doses and clinical impressions of efficacy are based on past publications of clinical trials, case series, and case reports,[40-55] and are largely covered in four reviews on the subject.[1,46,56,57] Single case reports and other studies that did not add substantive information were excluded, but drug classes and specific agents that have been commonly used to treat patients with PSH are covered in this table. Combinations of drugs are commonly used in clinical practice—eg, 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. PSH=paroxysmal sympathetic hyperactivity. *Drug administration routes are mainly intravenous or oral, which includes administration through a nasogastric or other feeding tube. The dose ranges listed cover the entire ranges that have been reported in the literature. The dosage and route of administration of drugs used should take into account each patient's individual circumstances and good clinical practice. †Evidence of efficacy is described as consistent when many or most of the publications reviewed showed benefits; intermediate when there was an equivocal impression of benefit in the literature; limited when data were scarce and inconclusive but showed some benefit; or ineffective when the literature showed no benefit. These judgments are subjective because a formal meta-analysis was not possible since the data are very heterogeneous and poorly documented. ‡Or other opioids; doses provided are for morphine.

***Table 2*: Classes of drugs used for treatment and prevention of PSH**

※参考　《 当院の自験例：25歳 女性（縊頸・低酸素脳症）》