Diagnosis and Treatment of Paroxysmal Sympathetic Hyperactivity in Medical ICU, University of Gondar Hospital, Northwest Ethiopia: A Case Report

Background: Paroxysmal sympathetic hyperactivity (PSH) is a neurologic syndrome characterized by paroxysmal and simultaneous occurrence of hypertension, hyperpyrexia, tachycardia, tachypnea, diaphoresis and dystonic posturing due to surge in sympathetic outflow after acquired brain injuries. Diagnosis of PSH is made using the paroxysmal sympathetic hyperactivity-assessment measure (PSH-AM) score, which comprises “clinical features severity” (CFS) score and “diagnosis likelihood tool” (DLT) score.

Case presentation: A 35-year-old woman diagnosed to have echo-proven chronic rheumatic heart disease for 25 years. Percutaneous balloon mitral valvotomy was done 6 weeks previously for severe mitral stenosis. Left atrial thrombus was detected after the procedure and anticoagulant (warfarin) was initiated. She presented with severe headache and repeated vomiting of 1 day duration on arrival to the hospital. She had frequent seizure attacks with subsequent loss of consciousness on third day of admission. Diagnosis of status epilepticus secondary to intracranial hemorrhage due to warfarin toxicity was made after CT-scan revealed acute subdural hematoma and ventricular bleeding. Then she was transferred to medical intensive care unit (ICU), intubated and put on mechanical ventilator. Anti-epileptic drugs, antibiotics, vitamin K and fresh frozen plasma were given. She developed paroxysms of hypertension, tachycardia, tachypnea, hyperpyrexia, diaphoresis and decerebrate posturing after 7 days of neurological insult. She had normal inter-ictal EEG tracing during cyclic autonomic surge. CFS score was 11 and DLT score was 10. In sum, PSH-AM score was 21, suggested “probable” diagnosis of PSH. Morphine, diazepam, propranolol and gabapentin were given in combination to treat PSH. Severity of autonomic storm started to improve on second week of ICU admission. On the third week of admission, her clinical condition deteriorated suddenly, she developed asystole and died of cardiac arrest despite cardiopulmonary resuscitation (CPR).

Conclusion: 'Clinical scoring' was used used to diagnose PSH, since there was no any confirmatory test. Cocktail of drugs were required to treat catecholamine surge in PSH.

Keywords: paroxysmal sympathetic hyperactivity; PSH, intracranial hemorrhage, warfarin toxicity

Background
Paroxysmal sympathetic hyperactivity (PSH) was first described as ‘diencephalic autonomic epilepsy’ by Wilder Penfield in 1929. The term “paroxysmal sympathetic hyperactivity” was first coined by Alejandro Rabinstein in 2007. It is a neurologic syndrome characterized by paroxysmal and simultaneous occurrence of...
hypertension, tachycardia, tachypnea, hyperpyrexia, dia-
phoresis and abnormal motor posturing due to surge in
sympathetic outflow after acquired brain injuries. Almost
all (95%) cases of PSH are caused by traumatic head
injury, anoxia and stroke. Since there is no con-
firmatory test, diagnosis of PSH is made using combi-
nation of “clinical features severity” (CFS) score and “diagnosis
likelihood tool” (DLT) score, named as PSH-AM (assessment
measure) score. The CFS score assesses presence and severity of clinical features, while the DLT measures
the presence of compatible clinical parameters (frequency, duration, paroxysms and simultaneity of hyper-sympa-
thetic episodes, antecedent cause, triggering factors, allo-
dynia, excluding alternative causes, and response to treatment). PSH contributes to troublesome clinical effects
including worst clinical outcome, physical disability, pro-
longed hospital stay and high cost for health care.6–10
Here, we discuss a case of PSH secondary to intracranial
hemorrhage after warfarin toxicity.

Case Presentation
A 35-year-old woman diagnosed to have echocardi-
ographic-proven chronic rheumatic heart disease (severe
mitral stenosis with pulmonary hypertension) for the past
25 years. She had undergone percutaneous balloon mitral
valvotomy (PBMV) 6 weeks previously. The left atrial
thrombus was detected after the procedure and she started
warfarin 5 mg, po, daily for 4 weeks and escalated to
7.5mg po daily to meet desired INR.

On her day of presentation to Emergency Medical
OPD, she had a severe headache and repeated episodes
of vomiting of ingested matter of 1 day duration. She gave
recent history of nasal bleeding, and stopped warfarin by
herself 3 days ago. She gave history of fever, malaise and
generalized weakness of 1 week duration.

On initial clinical evaluation, vital signs were within
normal limits and stable. She had no pallor of conjunctivae
and had wet buccal mucosa. On cardiovascular examination,
she had accentuated P2, mid-diastolic and pan-systolic mur-
mur at mitral area, but no summation gallop. No cranial nerve
palsy, no motor or sensory deficit, and meningeal irritation
signs were negative. Findings in other systems were unre-
markable. Diagnoses of chronic rheumatic heart disease
(mitral valve disease with pulmonary hypertension),
PBMV, left atrial thrombus, pyogenic meningitis R/o subar-
achnoid hemorrhage were made.

Laboratory values revealed white blood cell count (wbc)
=25,000/µL (neutrophil count=85%, lymphocyte count=10%),
hemoglobin (hgb)=12gm/dl, Platelets=350,000/µL. Liver
function tests (LFTs) and renal function tests (RFTs) were
within normal values. Blood culture was taken, but no growth
at first, second or seventh day of incubation. Coagulation
profiles showed prothrombin time (PT)=35 sec (normal
value=11–13 sec), partial thromboplastin time (PTT)=53 sec
(normal value=22–35 sec) and international normalized ratio
(INR)=2.5 (normal value=0.8–1.4) (Table-1). A lumbar
puncture was deferred due to higher INR value.
Electrocardiography (ECG) tracing showed P-mitrale, right
bundle branch block (RBBB), and ST depression and inverted
T wave at V1-V3, suggestive of left atrial enlargement and
right ventricular strain. Trans-thoracic echocardiography
revealed moderate mitral stenosis, mild mitral regurgitation,
and severe pulmonary hypertension. No vegetation or

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Note: NB: EMOPD, admission at Emergency Medical OPD; M-ICU, admission at Medical ICU.
thrombus was seen. She was initiated with Ceftriaxone 2gm, IV, twice daily and Vancomycin 1 gm, IV, twice daily, and warfarin was already discontinued.

On the third day of admission, she developed sudden onset, frequent tonic-clonic convulsive episodes with subsequent loss of consciousness. On physical examination, blood pressure (BP)=130/90 mmhg, pulse rate (PR)=116 beats per minute (bpm), respiratory rate (RR)=32 breaths per minute (bpm), temperature (T)=38.6 °C. There was transmitted sound all over the chest. A neurological examination revealed Glasgow Coma Score (GCS) of 8/15 (E2, M4, V2). Both eyes deviated to the left side. Pupils were mid-sized, but poorly reactive to light. She withdrew to painful stimuli. Meningeal irritation signs were negative. Diagnosis of status epilepticus secondary to intracranial hemorrhage due to warfarin toxicity was made after non-contrast brain CT scan revealed left-sided acute subdural hematoma and ventricular bleeds (Figures 1 and 2). Then, patient was initiated on diazepam, 10mg IV, and Phenytoin 1gm IV bolus followed by 100mg IV 3 times a day to arrest the seizure. She was given O₂ via face mask, NG-tube was inserted, and urinary catheter was put in situ.

She was transferred to ICU after a diagnosis of status epilepticus, was intubated and put on a mechanical ventilator. Vital signs and Spo₂ were monitored by cardiac telemetry. Fresh frozen plasma 4 units, and vitamin k, 10 mg IV once daily for 3 days were given. IV ceftriaxone and vancomycin were continued. Mannitol (20%), 50gm IV bolus and 25gm IV 3 times daily was provided to decrease increased intracranial pressure (ICP). Valproic acid, 400mg po 3 times daily was added as the seizure was poorly controlled. A craniotomy was done by neurosurgeon on the same day of neuroimaging and evacuated clots of blood.

Repeat laboratory values revealed WBC=34,000/µL (neutrophil count=85%, lymphocyte count=10%), hgb=9gm/dl, platelets=550,000/µL. Coagulation profiles showed PT= 49.8 sec (>3.5x ULN), PTT=63.2 sec (>1.5x ULN) and INR=4.38 (>3x ULN). Serum LFTs, RFTs and electrolytes were with in normal limits (Table 1).

Paroxysms of increase in pulse rate, blood pressure, respiratory rate, temperature, sweating, and decerebrate posturing became typical after 7 days of neurological insult. It occurred while suctioning, body turning, and physical examination. It occurred at least 2–4 times a day, each persisting for between 5 and 40 minutes. PSH was considered by neurologist after repeated recordings of normal inter-ictal EEG tracing during episodes of autonomic surge. CSF score was 11 (heart rate >140 beats per minute, respiratory...
rate=24-29 breaths per minute, systolic blood pressure=140-159 mmhg, temperature=38-38.9 ⁰c, mild sweating, and moderate posturing during episodes). DLT score was 11 (anteceend acquisition brain injury, sympathetic surges were paroxysmal, simultaneous, episodic and episodes occurred >2 times daily and persisted for > 2 weeks post-brain injury, provoked by non-painful stimuli (allodynia), and medicaions reduced sympathetic features). "Probable" diagnosis of PSH was made after patient scored 21 using PSH-AM score (sum of CFS score and DLT score). Then, she was adequately rehydrated with isotonic fluids; and started on morphine 2 mg, IV, as required (prn); paracetamol 1 gm, po as required (prn); propranolol, 40 mg po 3 times a day; diazepam 5 mg, IV 3 times a day; and gabapentin 150–300 mg po 3 times a day. Her GCS started to improve on second week of ICU admission, and frequency and severity of sympathetic storm declined. IV antibiotics were discontinued after 2 weeks of therapy. On the third week of admission, her clinical condition deteriorated all of a sudden, developed asystole, and died of cardiac arrest despite cardiopulmonary resuscitation (CPR).

Discussion

PSH is 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.

PSH is prevalent in young men, and incidence ranges from 8–33%. Higher incidence was reported in those with diffuse traumatic brain injury. Traumatic brain injury (80%), anoxic brain injury (10%), and cerebrovascular accidents (5%) took the majority of the share as etiology of PSH. The remaining 5% is caused by brain tumor, encephalitis, hydrocephalus and unspecified causes. 2-7,11,12

Although pathophysiology basis for PSH is incompletely understood, speculative explanations rest on "disconnection theory" and "excitation-inhibition ratio (EIR) model." Disconnection theory suggested a loss of inhibitory cortical centers control over caudal excitatory autonomic centers, while the EIR model proposed failure to modulate spinal cord excitatory sensory circuits by inhibitory centers within brainstem (the periaqueductal grey matter). 5-8

PSH manifests abruptly in cyclic episodes, either spontaneously or in response to unavoidable non-noxious stimuli, such as tracheal suctioning, urinary catheterization, and body positioning. It usually occurs 1 week after acquired brain injury. Paroxysms appear 3 to 5 times a day and each episode on average lasts for 30 minutes to 1 hour. Diagnosis of PSH is made by combination of “CFS” score and “DLT” score, named as PSH-AM (assessment measure) score. 6-10

Our patient presented with cyclic sympathetic storm with PSH-AM score of 21 after acquired brain injury, suggested "probable" diagnosis of PSH. Differential diagnosis for a patient presenting with altered mental status, muscle rigidity, hyperpyrexia and autonomic instability includes malignant hyperthermia, neuroleptic malignant syndrome, narcotic withdrawal syndrome, thyroid storm and encephalitis. Delayed onset of symptoms (~ 1 week) after exposure to anesthetic drugs; lack of exposure to neuroleptic drugs and narcotics; absence of preceding thyrotoxicosis features and normal thyroid function tests (TFTs); and CT-evidenced intracranial hemorrhage exclude likely differential diagnoses.

Uncontrolled PSH can lead to secondary brain injury with a worse GCS score, cardiac damage including arrhythmia and cardiomyopathy, and immunosuppression. It has been associated with increased infectious episodes, prolong hospital stay, worse functional independence, and higher health care costs. Although PSH was not a life threatening problem, it contributed to the death of this patient possibly due to arrhythmia with underlying cardiac disease. 6-8

Medical treatments for PSH include combinations of μ-opioid receptor agonist (morphine), non-selective β-receptor blocker (propranolol), α2-receptor agonist (clonidine), GABA-receptor agonist (gabapentin), dopamine-receptor antagonist (bromocriptine) and benzodiazipines (diazepam) to abort or minimize PSH episodes via inhibition of sympathetic flow, afferent sensory process and effector end organ response. 6-8,11-14 Early diagnosis and optimized treatment is believed to shorten ICU stay, facilitate patient recovery and minimize physical disability. In conclusion, 'clinical scoring' was used to diagnose PSH, since there was no any confirmatory test. Cocktail of drugs were required to treat catecholamine surge in PSH.

Abbreviations

BP, blood pressure; CT scan, computerized tomogram; CFS, clinical features severity; CPR, cardiopulmonary resuscitation; DLT, diagnosis likelihood tool; ECG, electrocardiogram; EEG, electroencephalogram; EMV, eye opening, motor response, verbal response; ESR, erythrocyte sedimentation rate; Hgb, hemoglobin; MICU, medical intensive care unit; ICP, intracranial pressure; INR, international normalized ratio; IV, intravenous; LFT, liver function test; MU,
million units; \( \text{O}_2 \), oxygen; OPD, outpatient department; PR, pulse rate; PO, per os; PSH, paroxysmal sympathetic hyperactivity; PBMV, percutaneous balloon mitral valvotomy; PSH-AM, PSH-assessment measure; PT, prothrombin time, PTT, partial thromboplastin time; RR, respiratory rate, RBBB, right bundle branch block; RFT, renal function test; \( \text{SpO}_2 \), arterial \( \text{O}_2 \) saturation; \( T^\circ \), temperature; WBC, white blood cell.

Ethics Approval and Consent to Participate
The authors declare that ethics approval was not required for this case report as we did not use any new procedures or any treatment, which was not approved for clinical use in our institution.

Consent for Publication
Written informed consent was obtained from the next-of-kin for publication of the case report and any accompanying images, since the patient died on the third week of admission in the hospital.

Acknowledgment
We are grateful to thank health personnel, who were taking care of the patient.

Author Contributions
All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure
The authors declare that they have no competing interests.

References