Paroxysmal sympathetic hyperactivity in hemispheric intraparenchymal hemorrhage

Billy Gao¹, Jeffrey A. Pollock², and Holly E. Hinson¹
¹Department of Neurology, Oregon Health & Science University, Portland, Oregon
²Department of Radiology, Oregon Health & Science University, Portland, Oregon

Abstract

Introduction—Paroxysmal sympathetic hyperactivity (PSH) is a hyperadrenergic syndrome that may follow acute brain injury characterized by episodic, hyperadrenergic alterations in vital signs. Identifying commonality in lesion localization in patients with PSH is challenging, but intraparenchymal hemorrhage (IPH) represents a focal injury that might provide insight. We describe a series of patients with IPH that developed PSH, and review the literature.

Methods—Patients with IPH who developed PSH were identified from OHSU hospital records. A literature review was conducted to identify similar cases through PUBMED, OVID, and Google Scholar.

Results—Three cases meeting criteria for PSH were identified. Hemorrhage volume ranged from 70 to 128 mL, and intracranial hemorrhage score ranged from 2 to 3. The laterality of the hemorrhage and significant volume of hemorrhage was similar in each of the patients, specifically all hemorrhages were large, subcortical, and right-sided. A literature search identified six additional cases, half of whom reported a right hemisphere hemorrhage and the majority also had subcortical localization.

Conclusions—Our literature review identified six cases of IPH associated with PSH with five cases having subcortical lesion locations, echoing the areas of disruption in our three cases. On the basis of these observations, we hypothesize that injuries along the pathway from the insular cortex to downstream sympathetic centers may remove tonic inhibition leading to unchecked sympathetic outflow. Prospective investigations of lesion location in patients with IPH and PSH are warranted to test this hypothesis, especially with advanced neuroimaging techniques.

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Correspondence Holly E. Hinson, Neurology and Neurocritical Care, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, CR-127, Portland, OR 97239. Tel/Fax: 503 418-1472; hinson@ohsu.edu.

Conflict of Interest
None declared.
Introduction

Paroxysmal sympathetic hyperactivity (PSH) is a clinical syndrome that may follow any type of acute brain injury (ABI). PSH most commonly occurs after traumatic brain injury (TBI), however, PSH has been known to follow both hemorrhagic and ischemic strokes. While there is no strict definition, conceptually PSH is best defined as an episodic entity consisting of the clinical features of increasing sympathetic drive including tachycardia, tachypnea, hypertension, fever, diaphoresis, and pupil dilation along with motor features such as decerebrate/decorticate posturing in the setting of severe neurologic injury that cannot be attributable to other causes.\textsuperscript{1,2} Even more poorly defined is the pathophysiology of PSH, however, some authors have proposed that that there is a release of higher inhibitory drive in the central nervous system that allows unchecked sympathetic outflow that causes the symptomatology of PSH.\textsuperscript{3,4}

Methods

All cases of intraparenchymal hemorrhage (IPH) admitted to the neurosciences intensive care unit at the Oregon Health and Science University were reviewed from June 2012 to December 2012. Patients met criteria for PSH when they developed paroxysmal events of vital sign abnormalities including tachycardia, hypertension, tachypnea, and hyperthermia spontaneously or in the setting of nonpainful stimuli. Duration was not used as an exclusion criterion. Patients were considered to have PSH if neuroleptic malignant syndrome, serotonin syndrome, autonomic dysreflexia, sepsis, pulmonary embolism, Cushing’s response, and withdrawal states were ruled out as causes. Etiology, Glasgow Coma Score (GCS) on admission, location, and volume of hemorrhage were ascertained along with calculated intracranial hemorrhage (ICH) scores based on initial presentation to the neurosciences intensive care units (NSICU). Available computed tomography (CT) images were coregistered over a template image to determine anatomical areas of overlap of the hemorrhages.

A literature review of cases of ICH and PSH was conducted using Pubmed, OVID, and Google Scholar. Search terms included “PSH, ICH, sympathetic, autonomic instability, and sympathetic storming.” Using available data from identified papers, we attempted to identify etiology, laterality, volume, location, GCS, and ICH scores.

Results

Three cases were identified from 66 total admissions of isolated, nontraumatic IPH (4.5%). The etiology of hemorrhage was different in each case, and included methamphetamine-related hypertension, right basal ganglia arteriovenous malformation (AVM), and therapeutic anticoagulation for cardiac mechanical valve. Hemorrhage volume ranged from 70 to 128 mL, and ICH score ranged from 2 to 3. The laterality of the hemorrhage and significant volume of hemorrhage was similar in each of the patients.
**Case 1**

A 50-year-old man was found unresponsive with right IPH in the right frontal lobe involving the caudate and putamen (72 mL) with midline shift on noncontrast head CT and an ICH score on admission of 3. He was hypertensive to 170 sec/90 sec mmHg with methamphetamine positive urinary drug screen (UDS) on presentation. The etiology of the bleed was thought to be due to hypertension given the location and history of illicit drug use. He underwent decompressive craniotomy with clot evacuation.

On the third day of admission, he developed intermittent febrile episodes up to 39.3°C, tachypnea to the 30 breaths per minute, sinus tachycardia to the 110 beats per minute, systolic hypertension up to 190 mmHg, and sustained upper extremity posturing. These episodes were stimulus responsive and spontaneous. An electroencephalogram (EEG) was negative for seizures. By hospital day five, he was noted to have fever up to 39.6°C. Panculture revealed enterobacter in the sputum but no clear infiltrate on the chest x-ray (CXR). Blood cultures were also negative. He was treated with broad-spectrum antibiotics which failed to modify sympathetic over activity. Fentanyl and gabapentin reduced the severity and frequency of episodes. He was transitioned to oral propranolol and clonidine, and frequency of events appeared to decrease with treatment. Unfortunately his course was complicated by multisystem organ failure, and the family decided to transition to comfort care, and the patient expired.

**Case 2**

A 37-year-old woman presented with severe headache, vomiting, and loss of consciousness with a large right IPH involving the putamen and with midline shift on noncontrast head CT. ICH score was 2. She underwent decompressive craniotomy with clot evacuation. The etiology was due to ruptured AVM in the right basal ganglia with feeding arteries from Recurrent Artery of Hubner and lenticulostriates, draining into the right transverse sinus. Four days post admission, she started to have stimulus-induced elevations in her blood pressure from systolic blood pressure (SBP) 100 to 140 sec, heart rate from 80 to 110 sec. Severity and frequency of symptoms responded to gabapentin. Ten days into the course, symptoms of PSH resolved and gabapentin was discontinued.

Her course was later complicated by infarcts in multiple areas including the right pons, left pons, posterior limb of the right internal capsule, splenium of the corpus callosum, right hemisphere, right corpus callosum, right caudate, and left frontal/temporal lobes. On discharge she was intermittently able to follow commands on her right upper extremity.

**Case 3**

The third patient was a 28-year-old woman with a history of Velocardiofacial DiGeorge Syndrome, Truncus Arteriosus Type I, and developmental delay. She was initially admitted with presumed methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteremia due to MSSA mechanical aortic valve endocarditis with fever, chills, and confusion. She was treated with a heparin infusion to prevent thrombus formation. Her course was complicated by a large right frontal IPH involving subcortical white matter and deep gray matter.
structures (128 mL) in the setting of a therapeutic range activated partial thromboplastin
time (aPTT). She underwent decompression and clot evacuation. ICH score was 2.

Two days after the hemorrhage, she started to have episodes of tachycardia up to the 130 sec
and fever up to 38.3°C in response to benign stimuli. Episodes were responsive to
dexmedetomidine infusion and she was transitioned to propranolol and gabapentin. Severity
and frequency of episodes decreased over the subsequent 4 days. Her examination remained
poor, and she was placed at a skilled nursing facility.

**Literature Review**

Seven manuscripts\textsuperscript{5–11} were identified reporting patients exhibiting both ICH and PSH
(Table 1). Only six cases reported the location of the hemorrhage. In some cases, the
hemorrhage volume or etiology was not identified. Etiologies of hemorrhage included
hypertension, postpartum hypertension, and anticoagulation use. Etiology, age, and gender
were varied. Three cases reported hemorrhage in the right basal ganglia, thalamus, and
“right parenchyma.” The three other cases with localizing data reported lesions in the left-
sided parenchyma (\(n = 2\)) and the pons (side unspecified, \(n = 1\)).

**Discussion**

**Location, laterality, and PSH**

We present a total of nine cases of IPH producing PSH, three from our institution and six
from the literature. While the cases are heterogeneous, some commonalities exist. Where
reported, hemorrhages were often large (>60 mL) and with devastating outcomes. The
damage frequently involved subcortical structures, and, where reported, occurred with
greater frequency on the right (six cases of right hemispheric IPH compared to two cases of
left hemispheric IPH). The three cases at our institution all had right hemispheric IPHs
located subcortically but rostral to the mesencephalon (Figs. 1, 2).

On the basis of these observations, we hypothesize that injuries along the pathway from the
insular cortex to downstream sympathetic centers may remove tonic inhibition coming from
that insular cortex leading to unchecked sympathetic outflow.

The model proposed by Baguley et al. of the excitatory: inhibitory ratio of sympathetic
outflow suggests several potential locations of injury that may differentially release
inhibition of sympathetic outflow.\textsuperscript{3} Baguley et al. propose that sympathetic outflow from
upstream sympathetic centers rostral to the mesencephalon are predominantly inhibitory to
spinal cord processes and that lesions downstream from these centers lead to disruption of
inhibition, allodynia and increased sympathetic tone. In this model, TBI can cause lesions in
different anatomical locations that are downstream of central sympathetic centers to present
with a common phenotype of increased sympathetic outflow. This model would be
compatible with the findings of Beattie et al. who found that tachyarrhythmias were stopped
by sectioning up to the mid collicular region of the diencephalon but not higher.\textsuperscript{12} The
pontine hemorrhage we identified in the literature is the only case less compatible with the
excitatory and inhibitory ratio model as the site of injury is downstream of the mesencephalon.

Based on the stroke and cardiac literature in humans and animals, the insular cortices have been implicated in sympathetic tone modulation, suggesting that this may be the source of upstream tonic inhibition to sympathetic tracts. In rat models, both the right and left insular cortices have shown to the have influence over autonomic function. Chemical lesions in the right posterior insula in the rat have been shown to increase blood pressure and heart rate.\textsuperscript{13,14} Left posterior stimulation and chemical lesions in the rat appear to alter baroreceptor sensitivity.\textsuperscript{15}

Although the data in humans is not as robust in regards to laterality, studies show that stimulation of the insula during epilepsy surgery appears to mirror the laterality seen in rats. Stimulation of the right anterior insula leads to elevated heart rate and diastolic blood pressure consistent with elevated sympathetic tone.\textsuperscript{16} Stimulation of the left caudal anterior insula increases bradycardia and depressor responses.\textsuperscript{16} A study by Oppenheimer et al. showed that patients with lesion in the left insular cortex had higher basal heart rate than age-matched gender controls.\textsuperscript{17} Oppenheimer has also identified that injury to adjacent right circumsulnsular cortex have led to abrogation of inhibition.\textsuperscript{18} These findings show that although both insular cortices affect sympathetic tone, they do so differentially.

The hemorrhages we identified were on the right side and our literature review of hemorrhages showed laterality that slightly favored right-sided injuries. It is possible that differential excitatory:inhibitory ratios exist in regards to the insular cortices; where inhibition of sympathetic outflow occurs in a less frequent manner in the left insular cortex compared to the right insular cortex.

Our case series is limited by a small number of patients. It may be coincidental that all three of our cases exhibited right hemispheric hemorrhages. Additionally, our search of the literature identified few cases of IPH and PSH. Efforts to identify all cases were likely hampered by the confusing nomenclature surrounding paroxysmal hyperactivity. The severity of injury in TBI must be grave for patients to develop PSH. For this reason, isolated, nontraumatic IPH may present a better patient population to identify lesion location, laterality, and risk of developing PSH. We propose that a future prospective study comparing patients with isolated hemorrhagic injuries with and without PSH be performed utilizing conventional and advanced imaging techniques including diffusion tensor imaging, as this may be helpful to clarify the role of location and laterality to the development of PSH.

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References

Figure 1.
Representative computed tomography images of cases 1–3.
Figure 2.
Overlay of cases 1–3 on a single image, with color representations of the overlapping areas of hemorrhage.
Table 1
Case series with literature review.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>GCS</th>
<th>Location</th>
<th>Volume</th>
<th>ICH score</th>
<th>Etiology</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>M</td>
<td>1-1T-5</td>
<td>R basal ganglia with frontal temporal extension, with IVH and MLS</td>
<td>72 mL</td>
<td>3</td>
<td>Hypertensive 2/2 methamphetamines</td>
<td>Death</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>F</td>
<td>1-1T-3</td>
<td>R basal ganglia, frontal temporal, MLS</td>
<td>70 mL</td>
<td>2</td>
<td>AVM</td>
<td>SNF placement</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>F</td>
<td>1-1-5</td>
<td>R basal ganglia, frontal temporal, MLS</td>
<td>128 mL</td>
<td>2</td>
<td>Therapeutic anticoagulation</td>
<td>SNF placement</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
<td>F</td>
<td>4</td>
<td>R thalamic</td>
<td>4 by 2.3 cm</td>
<td>NR</td>
<td>Suspected hypertension</td>
<td>NR</td>
</tr>
<tr>
<td>7</td>
<td>32</td>
<td>F</td>
<td>NR</td>
<td>L basal ganglia, with SAH and IVH</td>
<td>NR</td>
<td>NR</td>
<td>Suspected hypertension postpartum</td>
<td>NR</td>
</tr>
<tr>
<td>8</td>
<td>29</td>
<td>M</td>
<td>NR</td>
<td>L frontal</td>
<td>NR</td>
<td>NR</td>
<td>Warfarin, ischemic strokes prior of unknown etiology</td>
<td>Vegetative State</td>
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<tr>
<td>9</td>
<td>37</td>
<td>M</td>
<td>1-1-2</td>
<td>Pontine</td>
<td>NR</td>
<td>NR</td>
<td>Hypertension?</td>
<td>Nursing home</td>
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<tr>
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<td>54</td>
<td>M</td>
<td>NR</td>
<td>R basal ganglia</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>11</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>R intracerebral</td>
<td>NR</td>
<td>NR</td>
<td>Chronic vegetative state</td>
<td></td>
</tr>
</tbody>
</table>

AVM, arteriovenous malformation; IVH, intraventricular hemorrhage; L, left; MLS, midline shift; NR, not reported R, right; SAH, subarachnoid hemorrhage.