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Clinical characteristics, diagnostic challenges, and outcome of paroxysmal sympathetic hyperactivity in pediatric patients: a retrospective cohort study in a tertiary hospital setting

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Abstract

Introduction Paroxysmal Sympathetic Hyperactivity (PSH) is an under-recognized condition in pediatric patients, particularly those with non-traumatic brain injuries, often leading to delayed diagnosis and suboptimal management. The condition features episodic increases in sympathetic nervous system activity, which creates significant diagnostic and therapeutic challenges. This study aims to comprehensively characterize the clinical presentation, diagnostic challenges, and treatment outcomes of pediatric PSH in a tertiary care setting. Additionally, we investigate factors contributing to delayed diagnosis and assess the impact of various clinical and management variables on patient outcomes.

Methods This retrospective cohort study was conducted at King Abdullah Specialist Children's Hospital (KASCH), Riyadh, Saudi Arabia, encompassing 42 pediatric patients diagnosed with PSH between 2016 and 2023. We extracted comprehensive data from patient records, including demographic profiles, clinical presentations, diagnostic findings, and treatment outcomes. Statistical analyses were employed to identify factors influencing mortality and clinical improvement, including univariate and multivariate regression.

Results The cohort had a mean age of 6.53 years, with PSH onset typically around 4.19 years. The majority (88.1%) of PSH cases stemmed from non-traumatic causes, notably hypoxic-ischemic encephalopathy (31%). Key clinical features included fever, tachycardia, and dystonia, with a significant rate of initial misdiagnosis (69%). Healthcare providers frequently administer gabapentin as a preventive medication, while they commonly use benzodiazepines for abortive therapy. Clonidine use was associated with a statistically significant reduction in mortality ($P < 0.05$), whereas delayed diagnosis correlated with poorer clinical outcomes.

Conclusions PSH in pediatric patients predominantly arises from non-traumatic brain injuries, presenting with nonspecific symptoms that often lead to misdiagnosis. This study underscores the importance of early and accurate

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diagnosis in improving patient outcomes. Clonidine shows potential as a life-saving intervention in this context. These findings highlight the need for further research to refine diagnostic criteria and optimize treatment strategies for pediatric PSH.

Keywords Paroxysmal sympathetic hyperactivity, Sympathetic storm, Dysautonomia, Pediatric autonomic dysfunction

Paroxysmal sympathetic hyperactivity (PSH) syndrome frequently occurs in patients who have experienced brain injuries, such as traumatic brain injury (TBI), anoxic brain injury, stroke, tumors, infections, or other unspecified causes. The condition involves sudden, simultaneous, and temporary surges in sympathetic and motor activity in response to non-anxious stimuli.

The literature uses various terms to describe this syndrome, such as midbrain dysregulation syndrome, sympathetic storm, dysautonomia, diencephalic/mesencephalic seizures, and autonomic instability with dystonia [1]. PSH manifests in severe brain injury survivors through paroxysmal, transient bouts of heightened sympathetic activity leading to elevated heart rate, respiratory rate, sweating, blood pressure, temperature, and motor activity [2].

The pathophysiology of PSH needs to be explored more adequately in existing literature. Researchers believe structural damage disrupts the connections between higher cortical inhibitory brain regions and the brainstem or spinal/sympathetic centers, leading to the condition [3, 4].

Although the prevalence of PSH remains underresearched, estimates over the past decade suggest rates between 8% and 33% in adults, while limited pediatric data indicate a prevalence of 7–20% following various brain injuries. These variations highlight inconsistencies in diagnostic and admission standards and gaps in disease recognition [3, 5–8].

Clinically presenting symptoms of PSH are nonspecific and can lead to extensive diagnostic workup and occasional misdiagnosis. Symptoms include fever, increased heart and respiratory rates, elevated systolic blood pressure, sweating, and, in severe cases, dystonia and abnormal postures [2, 8, 9].

The Paroxysmal Sympathetic Hyperactivity Assessment Measure (PSH-AM) aids in diagnosis; however, its parameters are tailored for adult reference ranges, limiting its utility in pediatric cases. This limitation may delay diagnosis and potentially affect the management of PSH in children [2, 9, 10]. Imaging plays a limited role, with few nonspecific findings serving as potential markers for diagnosis or prognosis, such as damage to the corpus callosum or internal capsule posterior limb or the presence of diffuse lesions [10, 11].

The management of PSH involves both abortive and preventive pharmacological interventions. Morphine is the preferred abortive medication during episodes due to its demonstrated efficacy [3, 12]. Other options for both abortive and preventive purposes include clonidine and beta-blockers. However, it is important to note that gabapentin, a relatively new addition, has shown significant promise as a preventive measure that offers hope for reducing episode frequency and intensity, providing optimism in managing PSH [3, 13–15].

Research on PSH in pediatric populations remains scarce both locally and globally, leading to a limited understanding of its presentation, management, and prognosis, particularly in cases arising from non-traumatic brain injuries. The condition is marked by episodic increases in sympathetic nervous system activity, contributing to significant diagnostic and therapeutic challenges. This study aims to (1) delineate the clinical characteristics and symptom patterns of pediatric PSH; (2) analyze the diagnostic challenges that contribute to misdiagnosis and delayed intervention; (3) evaluate treatment strategies, including abortive and preventive pharmacotherapy; and (4) identify prognostic factors associated with mortality and clinical improvement. We seek to enhance awareness and optimize management approaches for pediatric PSH by addressing these gaps.

Methods

We conducted a retrospective cohort study of PSH children admitted to King Abdullah Specialist Children's Hospital (KASCH) in Riyadh, Kingdom of Saudi Arabia, established in June 2008. It is a tertiary care center and the first healthcare facility dedicated to children in Saudi Arabia. The hospital comprises 32 wards with a total bed capacity of 542 beds. The emergency department has 60 beds and manages approximately 100,000 visits per year. KASCH provides healthcare services to National Guard employees, soldiers, officers, and dependents. The study received approval from the Ethical Committee at King Abdullah International Medical Research Center (KAIMRC).

Eligibility criteria

We included pediatric patients under 14 years of age, irrespective of gender, who were admitted to KASCH from 2016 to 2023 with a diagnosis of PSH. Our team based this age threshold on institutional and national guidelines, which classify patients under 14 years as pediatric.

We excluded patients who had conditions during the initial symptomatic period that could mimic PSH symptoms, such as active seizures, sepsis, or meningitis. We based these exclusions on clinical assessments and positive culture results from cerebrospinal fluid, blood, urine, or respiratory secretions to avoid misclassifying symptoms caused by ongoing infection.

In addition, we excluded patients with incomplete medical records, defined as those missing one or more key elements required for analysis, including confirmed PSH diagnosis, clinical presentation, treatment details, or follow-up information. We excluded 29 patients based on this criterion. This selection process may limit the generalizability of our findings.

The classification of brain injuries followed definitions provided by the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH). These definitions describe traumatic brain injury (TBI) as resulting from an external physical force, while they categorize hypoxic-ischemic encephalopathy (HIE) due to birth asphyxia as a non-traumatic brain injury [16, 17].

Sampling technique

We utilized a non-probability consecutive sampling approach that included all patients with PSH admitted to KASCH between 2016 and 2023. This process involved a comprehensive analysis of medical records, allowing for the systematic documentation of presenting symptoms, laboratory results, and imaging findings.

Extracted data

By reviewing the electronic medical record system (Best Care), we extracted all relevant data, including (1) demographic characteristics such as age, gender, and background details; (2) We assessed clinical presentation, including autonomic dysfunction symptoms. We identified sleep disturbances by reviewing deviations from each patient's baseline sleep behavior, as documented in nursing flow charts and physician progress notes. These disturbances included difficulty initiating sleep, nighttime awakenings, and reduced total sleep duration. In high-dependency units, we also reviewed structured EMR tools that recorded observed sleep hours to support these observations; (3) diagnostic criteria application; (4) radiological findings such as echocardiography and brain imaging; (5) laboratory investigations such as complete blood count, inflammatory markers, and liver function tests; (6) treatment options, including both abortive and preventive medications, with doses administered according to recommendations of the Association for Pediatrics Palliative Medicine Formulary [18]; (7) associated risk factors for the development or exacerbation of PSH; (8) outcomes, including overall prognosis, complications, number of hospital admissions, and emergency department visits.

The clinical team monitored treatment compliance during the inpatient phase and documented observations in the electronic medical record. Their monitoring included tracking scheduled and PRN (as-needed) medication administration and the patient's clinical response. After discharge, they assessed parental compliance through caregiver reports during follow-up visits and through a dedicated support phone line provided to families. However, the retrospective nature of the study and potential documentation gaps limited the reliability of these assessment methods.

Statistical analysis

We analyzed the data using Jamovi software. The Shapiro-Wilk test indicated that the data did not follow a normal distribution. We reported the quantitative variables as means (with standard deviations) or medians (with interquartile ranges), and we described the qualitative variables in terms of their counts and frequencies. We performed descriptive analyses for all study variables and then conducted binomial univariate and multivariate regression analyses to examine mortality-related factors and clinical improvement.

Results

Baseline and demographic data

Our retrospective study, which provides a unique and in-depth analysis, included 42 PSH patients with a mean age of 6.53 years. Most patients were male (66.7%), born at term (90.5%), and had a global developmental delay (73.8%). A history of brain insult was present in 54.8% of cases, primarily due to hypoxic-ischemic encephalopathy (HIE) (31%), with non-traumatic causes accounting for 88.1% of PSH cases. Additionally, 81% of patients required a gastrostomy tube, and common comorbidities included epilepsy (66.7%), spasticity (90.5%), and gastroesophageal reflux disease (90.5%). Only two patients were initially diagnosed with PSH, while the majority were misdiagnosed, primarily as sepsis (69%), drug withdrawal (16.7%), or dystonia (11.9%). Table 1 and 2 show the baseline and demographic characteristics of the entire cohort.

Clinical presentation

Most patients exhibited key symptoms of sympathetic hyperactivity, including fever (92.9%), tachycardia (85.7%), tachypnea (97.6%), increased systolic blood pressure (73.8%), sweating (92.9%), dystonia (78.6%), and sleep disturbances (50%). Also, other symptoms were observed, like irritability, increased secretions, stridor, jitteriness, screaming, choreoathetosis movements, moaning and clenching teeth, neuropathic pain, and arching of the back. The mean frequency of PSH episodes per day

Table 1 Demographic and clinical characteristics of pediatric patients diagnosed with paroxysmal sympathetic hyperactivity

Variables (*N* = 42)	Counts	% of Total
Age in years		
Mean (SD)	6.53	3.883
Median (IQR)	6	(4, 9)
Age of PSH onset in years (*N* = 41)		
Mean (SD)	4.195	3.308
Median (IQR)	3	(2, 5)
Gender		
Male	28	66.7%
Female	14	33.3%
Gestational age		
Preterm	4	9.5%
Term	38	90.5%
Developmental status at the time of suspension of PSH		
Appropriate for age	11	26.2%
Global developmental delay	31	73.8%
History of brain insult		
Yes	23	54.8%
No	19	45.2%
Type of brain insult		
HIE	13	31.0%
Viral Encephalitis	1	2.4%
Autoimmune encephalitis	2	4.76%
Traumatic Brain Injury	5	11.9%
bacterial meningitis	1	2.4%
CHARGE syndrome with post-meningitis hydrocephalus	1	2.4%
None	19	45.2%
PSH Etiology		
Traumatic	5	11.9%
Non-traumatic	37	88.1%
Feeding		
Per oral	4	9.5%
Nasogastric tube	4	9.5%
Gastrostomy tube	34	81.0%
Comorbidities		
Epilepsy	28	66.7%
Spasticity	38	90.5%
GERD	38	90.5%

was 3.8 times, the mean Glasgow Coma Scale of included patients was 9.42, and the mean duration of hospital stay was 135.1 days. Table 3 shows the full details of the clinical presentations of the patients.

The most common misdiagnosis was sepsis, while other diagnoses were drug withdrawal symptoms, dystonic attack, respiratory infections, and complex regional pain syndrome; only in two patients was PSH diagnosis established first. Table 2 shows the full details.

Diagnosis and investigations

The research team applied the PSH-AM scale to 52.4% of the patients and calculated a mean score 21.05. They determined that the average time to diagnosis was 3.76 years after symptom onset. Most patients had unremarkable laboratory results: complete blood count in 78.6%, liver function tests in 61.9%, erythrocyte sedimentation rate in 50%, and C-reactive protein levels in 48.8%. Blood cultures returned negative in 88.1% of cases, urine cultures in 90.5%, cerebrospinal fluid (CSF) cultures in 64.3%, and respiratory cultures in 52.4%. Table 4 presents comprehensive diagnostic and investigation data.

Electrocardiograms (ECGs) showed normal findings in 50% of patients, while 21.4% had sinus tachycardia. Clinical teams did not perform ECGs in 23.8% of cases. Thirty-one patients had Echocardiograms (ECHOs), and 13 showed abnormalities: structural defects (20.9%), valvular disorders (4.7%), or functional impairments (4.8%). The team reviewed EEGs for 35 out of 42 patients. Among these, 35.7% showed background slowing, 9.5% showed interictal epileptic discharges, and 31% showed both findings. Tables 2 and 4 include these details.

Most patients underwent brain MRI, which revealed several key findings. The research team observed decreased brain volume in 26.19% of patients, hypoxic-ischemic encephalopathy (19.04%), demyelination (19.04%), diffuse axonal injury (7.14%), ischemic changes (19.04%)—including five old, one new, and one mixed—hemorrhage (7.14%), congenital anomalies (9.52%), autoimmune encephalitis (2.38%), and herniation (2.38%). Table 2 outlines these MRI findings in detail.

Due to the retrospective nature of the study and variability in initial clinical impressions, not all patients underwent a uniform set of investigations such as EEG, ECG, echocardiography, or brain imaging. This lack of standardized workup may limit the consistency of comparisons across patients and reduce the internal validity of some findings.

Abortive and preventive treatments

All patients received abortive medications. Clinicians most frequently prescribed benzodiazepines, which they used in 76.2% of cases. They also prescribed clonidine in 50%, morphine in 42.9%, and acetaminophen in 33.3% of patients. Other drugs were also used, such as beta-blockers (7.1%), ibuprofen (4.8%), and chloral hydrate (2.4%).

Regarding preventive medications, most of the patients were on preventive treatment (88.09%), and the most used drug was gabapentin in 71.4% of the patients, followed by baclofen in 38.1%, trihexyphenidyl in 14.3%, and pregabalin in 11.9%. Other drugs were used, like dantrolene (7.1%), diazepam (2.4%), chloral hydrate (2.4%), tetrabenazine (2.4%), and melatonin (2.4%). Table 5 shows the full details of used drugs with their dosage.

Table 2 Diagnostic and clinical profile of pediatric patients with paroxysmal sympathetic hyperactivity

ID	History of brain insult	Type of brain insult	Primary diagnosis	Other comorbidities	First impression (Misdiagnosis)	MRI brain findings	EEG Findings	ECHO
1	Yes	Traumatic Brain Injury	Traumatic brain injury	SIADH, Pneumothorax, GERD	Sepsis	hemorrhage & herniation	Not done	Not done
2	Yes	HIE	HIE due to perinatal asphyxia	Dysmorphism and Hypotonia, GERD	Sepsis	Ischemic changes	Slow background	Normal
3	Yes	Viral Encephalitis	Lymphoma	Lymphoma, GERD	Sepsis	volume loss	Slow background	Structural
4	Yes	HIE	Cardiac arrest secondary to anaphylaxis	NR	Sepsis	hemorrhage & ischemic changes (Extensive encephalomalacia, Necrosis of thalami, subdural collections)	slow background with epileptiform discharges	Not done
5	Yes	Autoimmune encephalitis	Anti-NMDA encephalitis	GERD	Sepsis and drug withdrawal symptoms.	volume loss	Seizure	Structural
6	Yes	HIE	HIE secondary to anoxic brain injury	Humeral fracture, GERD	Sepsis	profound HIE	Not done	Normal
7	No	None	Unknown autoimmune disease	GERD	Sepsis	volume loss	Slow background	Normal
8	No	None	Allen-Herndon syndrome	Central hypothyroidism, GERD	Sepsis	Demyelination	Not done	Normal
9	No	None	Neurodegenerative disease with no identified etiology	Hypotonia, scoliosis, GERD	Others (Pneumonia)	volume loss	Slow background	Normal
10	Yes	Traumatic Brain Injury	Traumatic brain injury	Scoliosis	Sepsis	Diffuse axonal injury	Slow background	Structural
11	Yes	HIE	HIE due to perinatal asphyxia	GERD	Sepsis	profound HIE	Slow background	Normal
12	No	None	HIE secondary to cardiac arrest	Truncus arteriosus, GERD	Sepsis	Ischemic changes	Slow background	Valvular
13	Yes	HIE	HIE due to near drowning	GERD	Dystonia	Ischemic changes	slow background with epileptiform discharges	Normal
14	No	None	Developmental regression since 4 months with no primary cause	GERD	Others (Fracture)	volume loss and demylination	slow background with epileptiform discharges	Normal
15	No	None	Neuronal ceroid lipofuscinoses type 7	GERD	Sepsis	volume loss	Slow background	Not done
16	No	None	Wilson's disease	Dystonia and choreoathetosis	Dystonia	Diffuse axonal injury	Not done	Normal
17	Yes	post-meningitis hydrocephalus	meningitis	Cholistaisis, hypoglycemia, developmental dysplasia of the hip, hepatomegaly, osteopenia, hiatal hernia, thrombocytopenia, and vesicoureteral reflux, GERD	Sepsis and ventriculoperitoneal shunt malfunction	Congenital anomaly	slow background with epileptiform discharges	Structural
18	No	None	No clear diagnosis	Sulphosystinurea, scoliosis, restricted lung disease, and microcephaly, GERD	Hospital-acquired pneumonia and sepsis	volume loss	Slow background	Normal

Table 2 (continued)

ID	History of brain insult	Type of brain insult	Primary diagnosis	Other comorbidities	First impression (Misdiagnosis)	MRI brain findings	EEG Findings	ECHO
19	Yes	HIE	No clear diagnosis but had HIE &other comorbidities.	Cleft palate, cardiac arrest, developmental dysplasia of the hip, swallowing dysfunction, and spina Bifida occulta, GERD.	Sepsis and central hyperthermia	profound HIE	slow background with epileptiform discharges	Structural
20	No	None	No diagnosis of genetic workup negative	Hypotonia, DVT, Chronic lung disease, GERD	Sepsis	Demyelination	Slow background	Normal
21	Yes	HIE	HIE near drowning	GERD	Sepsis and drug withdrawal symptoms.	profound HIE	slow background with epileptiform discharges	Not done
22	Yes	Traumatic Brain Injury	Traumatic brain injury	Stable Hydrocephalus, GERD	Sepsis, seizure, and pheochromocytoma.	Ischemic changes	slow background with epileptiform discharges	Normal
23	No	None	Vanishing white matter disease (Leukodystrophy)	Leukodystrophy and constipation hepatomegaly, GERD	Status dystonic and sepsis	Demyelination	Slow background	Normal
24	No	None	Chromosome 11 duplication syndrome	Holoprosencephaly, laryngomalacia, recurrent UTI (Extended-spectrum beta-lactamase Escherichia coli), recurrent aspiration pneumonia, hip dislocation, and central diabetes insipidus, GERD	Sepsis and central hyperthermia	Congenital anomaly	Slow background	Structural
25	Yes	Traumatic Brain Injury	Traumatic brain injury	On ventriculoperitoneal shunt, sialorrhea, and recurrent aspiration pneumonia, GERD	Sepsis	Ischemic changes	slow background with epileptiform discharges	Not done
26	Yes	Bacterial meningitis	bacterial meningitis Arnold Chiari malformation	Arnold Chiari malformation type two with myelomeningocele, congenital hydrocephalus on ventriculoperitoneal shunt, failure to thrive, right femur fracture, developmental dysplasia of the hip, neurogenic bladder, and vesicoureteral reflux, GERD	Sepsis and central hyperthermia	Congenital anomaly	Not done	Normal
27	Yes	HIE	HIE due to poststrangulation	Acute kidney injury, pulmonary embolism, GERD, and pneumothorax	Drug withdrawal symptoms.	profound HIE	Not done	Not done

Table 2 (continued)

ID	History of brain insult	Type of brain insult	Primary diagnosis	Other comorbidities	First impression (Misdiagnosis)	MRI brain findings	EEG Findings	ECHO
28	No	None	AR early infantile epileptic encephalopathy type76	GERD, AR early infantile epileptic encephalopathy type76 and dystonia microcephaly	Sepsis	Demyelination	Seizure	Functional
29	No	None	Anti-NMDA encephalitis	Elevated liver transaminases, GERD	Sepsis and drug withdrawal symptoms.	volume loss	slow background with epileptiform discharges	Normal
30	No	None	Panhypopituitarism	Panhypopituitarism, GERD	Sepsis	volume loss	slow background with epileptiform discharges	Structural
31	Yes	HIE	HIE due to perinatal asphyxia	GERD	Sepsis	Ischemic changes	slow background with epileptiform discharges	Not done
32	No	None	Immunodeficiency	Immunodeficiency, GERD	Sepsis	demylination (hypomyelination)	Normal	Structural
33	Yes	HIE	HIE due to near drowning	On tracheostomy, GERD	Drug withdrawal symptoms.	profound HIE	Seizure	Normal
34	No	None	Fever of unknown origin with negative extensive workup & negative trio WGS.	GERD, Hypotonia, difficult airway on home oxygen, and dysmorphic features	Septic shock due to pneumonia, fever of unknown origin, and periodic fever syndrome.	volume loss and demylination	slow background with epileptiform discharges	Structural
35	No	None	Leukodystrophy with ACER3 gene mutation.	Leukodystrophy, bronchial asthma, GERD, and neurogenic bladder with recurrent UTI	Sepsis	Demyelination	Slow background	Normal
36	Yes	Autoimmune encephalitis	Febrile infection-related epilepsy syndrome (FIRES) / New-onset refractory status epilepticus (NORES)	Constipation, GERD	Drug withdrawal symptoms.	autoimmune enchephalitis	Seizure	Not done
37	Yes	Traumatic Brain Injury	Traumatic brain injury	Multiple fractures, GERD, and liver laceration	Drug withdrawal symptoms.	hemorrhage and diffuse axonal injury	Normal	Not done
38	Yes	HIE	HIE post-cardiac arrest (near drowning)	GERD, Right femur fracture (osteopenia post physical therapy session)	PSH	volume loss	slow background with epileptiform discharges	Not done
39	Yes	HIE	HIE post-cardiac arrest (near drowning)	GERD, Constipation	PSH	profound HIE	Slow background	Not done
40	No	None	Dilated cardiomyopathy and extensive venous thrombosis.	Dilated Cardiomyopathy and Fever of unknown origin	Complex regional pain syndrome	Ischemic changes	Not done	Functional
41	No	None	Mitochondrial disease	GERD, Mitochondrial disease and osteopenia	Dystonia and fracture.	Congenital anomaly	Slow background	Normal
42	Yes	HIE	HIE	GERD, Dysmorphism, hypotonia and dysplastic pulmonary valve	Dystonia and respiratory infection	profound HIE	Normal	Valvular

Table 3 Symptom frequency and clinical metrics in pediatric patients with paroxysmal sympathetic hyperactivity

Variables	Counts	% of Total
Symptoms (*N* = 42)		
Fever	39	92.9%
Increased HR	36	85.7%
Increased RR	41	97.6%
High SBP	31	73.8%
low SBP	2	4.8%
Sweating	39	92.9%
Dystonia	33	78.6%
Sleep disturbance	21	50.0%
Irritability	19	45.2%
Increased secretions	9	21.4%
Moaning and clenching teeth	5	11.9%
Stridor	3	7.1%
Jitteriness	3	7.1%
Screaming	1	2.4%
Choreoathetoid movements	1	2.4%
Neuropathic pain	1	2.4%
Arching of back	1	2.4%
Frequency of episodes per day (*N* = 40)		
Mean (SD)	3.8	2.472
Median (IQR)	3	(2, 6)
Duration of episodes per day in minutes (*N* = 38)		
Mean (SD)	220.3	153.49
Median (IQR)	180	(120, 345)
GCS (*N* = 42)		
Mean (SD)	9.42	2.002
Median (IQR)	9	(9, 10)
Length of stay in days (*N* = 42)		
Mean (SD)	135.1	182.103
Median (IQR)	68	(28.5, 150)

Follow-up and outcomes

The mean number of follow-up visits was three, and the maximum interval between mean follow-up visits was 40.56 days. Most of the patients showed clinical improvement (87.5%), the mean interval between episodes reached 39.2 days, most of them had no complication to medications (61.9%), and the most reported complication was sedation (16.6%). Most patients were discharged home (90.2%), the mean number of emergency department visits after starting treatment was 4.75, and the mean number of hospital admissions was 4.7. The mortality rate was 34.1% of the patients. Table 6 shows the full details of the clinical outcomes of included patients.

Factors associated with increased risk of mortality and no clinical improvement

We performed binomial regression analysis to investigate factors associated with increased mortality. We found that older age and use of clonidine drug as abortive treatment were associated with decreased mortality risk in univariate ($P = 0.038$ and $P = 0.045$, respectively) and multivariate regression analyses ($P = 0.035$ and $P = 0.043$, respectively). Table 7 shows full details.

The univariate binomial regression analysis revealed a significant association between late diagnosis and decreased clinical improvement ($P = 0.033$). Table 8 presents full details.

Discussion

Our observational study included 42 pediatric patients diagnosed with PSH, with a mean age of 6.53 years. Most patients had a prior history of brain insult (54.8%), predominantly due to hypoxic-ischemic encephalopathy (HIE, 31%), and the majority had a global developmental delay before symptom onset (73.8%). Clinicians initially faced challenges in diagnosing PSH and accurately diagnosed only two patients during the first encounter. Common clinical presentations included fever, tachycardia, tachypnea, increased blood pressure, sweating, dystonia, and sleep disturbance. Although EEG and MRI frequently revealed abnormalities, these findings were generally nonspecific and reflected underlying neurological injuries rather than directly causing PSH episodes. This observation aligns with previous studies reporting nonspecific or diffuse abnormalities on brain imaging, such as susceptibility-weighted MRI and CT scans, in patients with PSH or dysautonomic crises [19–21].

Limited data on PSH characteristics in pediatric populations [3, 5–8] prompted this study to provide detailed epidemiological insights and to investigate factors influencing clinical improvement and mortality. Our findings indicate that non-traumatic etiologies, primarily hypoxic-ischemic encephalopathy (HIE), were more common in our cohort, whereas some pediatric-focused studies have reported traumatic brain injury (TBI) as a frequent cause of PSH [8]. While adult literature consistently attributes PSH to TBI [2, 22, 23], pediatric cases have also been linked to encephalitis and HIE [7, 24, 25], highlighting important age-related differences in etiology. This variation underscores the heterogeneity of pediatric PSH and the need for further research to clarify these discrepancies. While hypoxic-ischemic encephalopathy (HIE) can cause severe and long-lasting neurological sequelae, we classified it as a non-traumatic brain injury based on CDC and NIH definitions. These definitions distinguish HIE from traumatic brain injury (TBI), which results from an external force [16, 17]. Our regression analysis found no significant association between the type of brain insult and PSH prognosis, aligning with Pozzi et al. (2017), who reported no direct link between etiology and clinical severity or outcomes [26–28]. Although males predominated in our cohort, as observed in prior studies [25, 28, 29], gender did not significantly influence clinical outcomes.

Table 4 Diagnostic assessment and laboratory findings in pediatric patients with paroxysmal sympathetic hyperactivity

Variables (*N* = 42)	Counts	% of Total
PSH-AM use		
Performed	22	52.4%
Not done	20	47.60%
PSH-AM score (*N* = 22)		
Mean (SD)	21.05	6.904
Median (IQR)	21	(17, 24)
Onset of diagnosis		
Mean (SD)	3.76	2.92
Median (IQR)	2.96	(1.71, 5)
CBC		
Normal	33	78.6%
Abnormal	9	21.4%
LFT		
Normal	26	61.9%
Abnormal	16	38.1%
ESR		
Normal	21	50.0%
Abnormal	15	35.7%
Not done	6	14.3%
CRP (*N* = 41)		
Normal	20	48.8%
Abnormal	17	41.5%
Not done	4	9.8%
Blood culture		
Normal	37	88.1%
Abnormal	5	11.9%
Urine culture		
Normal	38	90.5%
Abnormal	4	9.5%
CSF culture		
Normal	27	64.3%
Abnormal	1	2.4%
Not done	14	33.3%
Respiratory culture		
Normal	22	52.4%
Abnormal	11	26.2%
Not done	9	21.4%
ECG findings		
Normal	21	50.0%
Not done	10	23.8%
Sinus tachycardia	9	21.4%
Sinus rhythm with 1st degree block	1	2.4%
Right bundle branch block	1	2.4%
EEG findings		
Normal	3	7.1%
Not done	7	16.7%
Slow background	15	35.7%
Slow background with epileptiform discharge	13	31%
Seizure	4	9.5%
MRI findings		
Ischemic changes	8	19.04%
hemorrhage	3	7.14%
herniation	1	2.38%
volume loss	11	26.19%
profound HIE	8	19.04%
Demyelination	8	19.04%
Diffuse axonal injury	3	7.14%
Congenital anomaly	4	9.52%
autoimmune encephalitis	1	2.38%
ECHO findings		
Normal	18	41.9%
Not done	11	25.6%
Abnormal	13	30.9%
Structural	9	20.9%
Valvular	2	4.7%
Functional	2	4.8%

The most frequent symptoms of PSH were fever, tachycardia, tachypnea, increased blood pressure, sweating, dystonia, and sleep disturbance, consistent with previous reports [28, 30]. However, the diagnosis of PSH remains complex. The PSH Assessment Measure (PSH-AM) is a diagnostic tool designed to aid in identifying PSH [2]. It consists of the Clinical Feature Scale, which assesses the severity of sympathetic signs, and the Diagnostic Likelihood Tool, which evaluates the certainty of PSH diagnosis. The reliability and feasibility of the PSH-AM have been validated [9], making it a valuable tool for reducing misdiagnosis, shortening hospitalization, and lowering costs [10]. The Clinical Feature Scale can monitor episodic severity or treatment efficacy [3, 14]. However, our regression analysis found no association between PSH-AM scores and mortality or clinical improvement, highlighting the need for further studies to resolve this controversy.

Diagnosing PSH remains challenging due to symptom overlap with various severe systemic and neurological disorders [31, 32]. Frequently, diagnosis occurs in intensive care settings, where multiple potential causes of autonomic instability exist [32]. Early identification is critical, as it can prevent unnecessary treatments and reduce complications. Our findings reinforce this, as delayed diagnosis was significantly associated with reduced clinical improvement [3].

In our cohort, PSH was frequently misdiagnosed as sepsis, dystonia, respiratory infections, or drug withdrawal — reflecting the diagnostic complexity noted in prior studies [3]. In particular, sepsis shares overlapping features with PSH, such as fever, tachycardia, tachypnea, and autonomic dysregulation, especially in critically ill patients. However, most of our patients had normal inflammatory markers and negative cultures, supporting a diagnosis of PSH rather than active infection. These diagnostic challenges have been consistently reported in

Table 5 Pharmacological management of paroxysmal sympathetic hyperactivity: abortive and preventive medications and dosages

Variables	Used dosage	Counts	% of Total
Abortive medications use			
Number of patients on abortive treatment	42	100%	
Morphine	0.03 to 0.5 mg/kg every (6–8 h)	18	42.9%
Clonidine	0.001 to 0.005 mg/kg every (6, 8, or 12 h)	21	50.0%
Benzodiazepine	0.03 to 1 mg/kg every (6, 8, or 12 h)	32	76.2%
Acetaminophen	10 or 15 mg/kg every (8 h)	14	33.3%
Beta-blocker	0.05 to 2.3 mg/kg every (6–8 h)	3	7.1%
Ibuprofen	10 mg/kg every (8–48 h)	2	4.8%
Chloral hydrate	25 mg/kg every 8 h	1	2.4%
Preventive medication			
Number of patients on preventive treatment		37	88.09%
Gabapentin	10 to 50 mg/kg, every (8, 12, or 24 h)	30	71.4%
Baclofen	0.5 to3 mg/kg, every (8–12 h)	16	38.1%
Trihexyphenidyl	0.6 to 2 mg/kg every (8–12 h)	6	14.3%
Pregabalin	3, 5.5, 40, 50 mg/kg every (8, 12, or 24 h)	5	11.9%
Dantrolene	1 mg/kg, every (8–12 h)	3	7.1%
Diazepam	0.05 mg/kg every 6 h	1	2.4%
Chloral hydrate preventive	0.5 mg/kg every 12 h	1	2.4%
Tetrabenazine	0.6 mg/kg every 12 h	1	2.4%
Melatonin	0.4 mg/kg every 24 h	1	2.4%

the literature, highlighting the importance of careful clinical evaluation [2, 3].

Similarly, complex regional pain syndrome (CRPS) may present with autonomic features, including sweating and vasomotor instability, that can resemble aspects of PSH. Although CRPS is typically a localized pain syndrome with distinct sensory and trophic changes, the autonomic hyperactivity seen in PSH—particularly when accompanied by dystonia or rigidity—can mimic CRPS-like presentations, especially in children. The episodic and systemic nature of PSH, along with hallmark signs such as persistent hyperthermia and generalized sympathetic activation, can help distinguish it from CRPS [14].

Laboratory assessments in our group revealed normal findings for CBC, CRP, ESR, and cultures, which help distinguish PSH from infectious causes, where we would anticipate abnormal lab results. EEG primarily showed slow background activity rather than epileptiform discharges, consistent with previous studies suggesting that PSH episodes result from cortical-subcortical dysfunction rather than epileptic activity [33–35].

To effectively manage PSH, healthcare providers use a combination of abortive and preventive therapies. To effectively manage PSH, healthcare providers use a combination of abortive and preventive therapies [36, 37]., and some drugs function as both abortive and preventive therapies, like clonidine and beta-blockers [15, 36]. In our cohort, benzodiazepines were the most frequently utilized abortive therapy (76.2%), gabapentin was the most used preventive therapy (71.4%), and morphine was used as abortive medication in 42.9% of patients, aligning with recommendations in existing literature [15, 36]. Most patients clinically improved (87.5%), and most experienced no complications (61.9%). However, the mortality rate was notably high at 34.1%, despite various therapeutic approaches, emphasizing the severity of PSH in pediatric patients. In regression analysis, clonidine was uniquely associated with a significant reduction in mortality, highlighting its potential benefit in pediatric PSH management due to its central α-2 adrenergic receptor-mediated effects on sympathetic activity [3, 15]. However, clonidine's possible side effects, including sedation, hypotension, and bradycardia, should be carefully monitored. Other medications, including morphine, benzodiazepines, and gabapentin, did not demonstrate a statistically significant impact on mortality outcomes. Increasing patient age and clonidine use were associated with a decreased risk of mortality, whereas delayed diagnosis was significantly associated with reduced clinical improvement. Given our study's observational nature and limited sample size, these findings necessitate further prospective, multicenter studies to confirm clonidine's efficacy and define optimal dosing regimens.

Complementary non-pharmacological interventions also play an essential role in comprehensive PSH management. Environmental modifications serve as crucial first-line strategies before initiating therapeutic interventions. Regulating room temperature to minimize external stimuli and establishing a structured daily care routine can reduce hyperthermic episodes and mitigate autonomic dysregulation in PSH patients [38]. Letzkus et al. reported a significant association between

Table 6 Clinical outcomes and Follow-Up metrics for pediatric patients with paroxysmal sympathetic hyperactivity

Variables	Counts	% of Total
Number of FU visits (*N* = 40)		
Mean (SD)	3.075	3.3
Median (IQR)	2	(0.75, 4)
Maximum interval between FU visit/days (*N* = 37)		
Mean (SD)	40.5676	35.619
Median (IQR)	30	(21, 60)
Response (*N* = 40)		
Improved	35	87.5%
No change	5	12.5%
Interval between episodes (*N* = 31)		
Mean (SD)	39.2581	31.83
Median (IQR)	30	(21, 60)
Mortality (*N* = 41)		
Yes	14	34.1%
No	27	65.9%
Complications		
none	26	61.9%
Yes	16	38.1%
sedation	7	16.6%
Bradycardia	4	9.5%
mildly elevated liver transaminase	2	4.8%
Increased secretions	2	4.8%
DCL	2	4.8%
Hypotension	1	2.4%
Weight gain	1	2.4%
Respiratory depression	1	2.4%
urinary retention	1	2.4%
Ongoing admission (*N* = 41)		
Ongoing admission	4	9.8%
Discharged	37	90.2%
Number of hospital admissions (*N* = 37)		
Mean (SD)	3.6757	4.865
Median (IQR)	2	(0, 5)
Number of ER visits (*N* = 37)		
Mean (SD)	4.7568	6.26
Median (IQR)	2	(0, 8)

environmental temperature and PSH incidence, highlighting the increased risk associated with lower room temperatures and blanket use [39]. Additionally, hyperbaric oxygen therapy (HBOT) has shown promising preliminary results as an adjunctive therapy alongside conventional pharmacologic treatments, warranting further investigation into its potential therapeutic benefits [40]. A systematic review highlighted the significance of neurological stimulation and non-pharmacological rehabilitation interventions, including structured sensory modulation, multidisciplinary rehabilitation, and environmental modifications, in reducing autonomic dysregulation and enhancing patient recovery. These strategies are essential adjuncts to pharmacological management and should be integrated into comprehensive PSH treatment protocols to optimize patient outcomes [30, 41].

Strengths and limitations

Our study's primary strength lies in its focus on a rare and under-researched pediatric condition. It provides novel insights into the clinical characteristics, diagnostic challenges, and outcomes associated with paroxysmal sympathetic hyperactivity (PSH). By examining factors influencing clinical progression and mortality in pediatric patients, this study adds meaningful contributions to a field with limited data.

However, several limitations warrant consideration. First, the retrospective design introduces inherent selection and information bias, as it relies on the accuracy and completeness of medical records, which can vary between patients. Nonetheless, given the rarity and under-recognition of PSH—particularly in non-traumatic brain injury cases—a retrospective approach was the most feasible method to capture relevant clinical data. Many patients presented in critical condition, were admitted under various specialties and underwent extensive diagnostic evaluations before clinicians considered PSH, which limited the practicality of prospective data collection. This methodology is consistent with prior studies, including that by Alofisan et al. (2019), which used a similar approach.

Second, the absence of a control group limits our ability to draw causal inferences regarding PSH risk factors, treatment efficacy, or outcomes. Future research incorporating well-matched control groups and prospective designs is needed to establish more robust, evidence-based conclusions.

Third, not all patients underwent a uniform set of investigations (e.g., EEG, ECG, echocardiography, or brain imaging), which may reduce the comparability and internal validity of some findings. This variability reflects real-world clinical complexity but remains a methodological limitation.

Fourth, as a single-center study conducted at King Abdullah Specialist Children's Hospital (KASCH), the generalizability of our findings may be limited, particularly in healthcare settings with differing resources, protocols, or patient populations. Multicenter studies are needed to validate these observations and improve external applicability.

Fifth, the small sample size (42 patients) further reduces statistical power and may obscure smaller associations or treatment effects. Additionally, we analyzed a limited range of clinical variables, primarily those documented in the electronic medical records, and did not assess long-term neurodevelopmental outcomes, quality of life, or psychosocial impact.

Table 7 Regression analysis of predictive factors for clinical outcomes in pediatric paroxysmal sympathetic hyperactivity

Predictor	Univariate regression analysis				Multivariate regression analysis			
	Estimate	95% Confidence Interval		*p*	Estimate	95% Confidence Interval		*p*
		Lower	Upper			Lower	Upper	
Age	-0.25	-0.482	-0.0176	0.035	-0.279	-0.544	-0.0151	0.038
Female patients	-0.925	-2.41	0.565	0.224	-	-	-	-
Term	-18.6	-3896	3858	0.993	-	-	-	-
Global developmental delay	1.1	-0.599	2.796	0.205	-	-	-	-
Positive History of brain insult	-0.818	-2.13	0.497	0.223	-	-	-	-
Traumatic etiology	-0.816	-3.11	1.479	0.486	-	-	-	-
Age of onset	-0.246	-0.519	0.0262	0.076	-	-	-	-
Frequency (episodes per day)	0.126	-0.144	0.3967	0.361	-	-	-	-
Duration of attacks per day in minutes	-0.00447	-0.0104	0.00142	0.137	-	-	-	-
PSH-AM score	0.122	-0.0393	0.284	0.138	-	-	-	-
Onset of diagnosis	-0.064	-0.293	0.165	0.584	-	-	-	-
Abortive medications								
Morphine use	0.818	-0.497	2.134	0.223	-	-	-	-
Clonidine use	-1.45	-2.845	-0.0488	0.043	-1.576	-3.115	-0.0373	0.045
Benzodiazepine use	0.927	-0.783	2.637	0.288	-	-	-	-
Acetaminophen use	0.105	-1.25	1.46	0.879	-	-	-	-
Preventive medications								
Gabapentin use	1.1	-0.599	2.796	0.205	-	-	-	-
Baclofen use	-0.693	-2.08	0.693	0.327	-	-	-	-

Table 8 Univariate regression analysis of factors influencing clinical outcomes in pediatric PSH patients

Predictor	Univariate regression analysis			
	Estimate	95% Confidence Interval		*p*
		Lower	Upper	
Age	0.221	-0.0333	0.475	0.088
Female patients	-18.13	-5651.32	5615.062	0.995
Term	-0.981	-3.47	1.51	0.44
Global developmental delay	0.47	-1.84	2.78	0.69
Positive History of brain insult	-1.79	-4.08	0.501	0.126
Age of onset	0.234	-0.0626	0.531	0.122
Traumatic etiology	-16.74	-6408.81	6375.327	0.996
Frequency (episodes per day)	-0.42	-1.14	0.298	0.252
Duration of attacks per day in minutes	0.00534	-6.97e – 4	0.0114	0.083
PSH-AM score	-0.115	-0.46	0.23	0.513
Onset of diagnosis	0.38	0.0303	0.73	0.033
Abortive medications				
Morphine use	0.811	-1.1	2.724	0.406
Clonidine use	-0.577	-2.49	1.331	0.553
Benzodiazepine use	0.17	-2.16	2.5	0.886
Acetaminophen use	-0.86	-3.16	1.436	0.463
Preventive medications				
Gabapentin use	0.325	-1.99	2.644	0.783
Baclofen use	-1.1	-3.39	1.193	0.347

Sixth, post-discharge compliance was assessed indirectly through caregiver reports and follow-up documentation, which introduces the potential for recall and reporting bias. Similarly, inconsistencies in historical documentation prevented us from reliably determining the exact interval between the initial brain insult and the onset of PSH symptoms.

Lastly, in line with other retrospective studies, incomplete follow-up or documentation gaps may affect outcomes such as hospital admissions, emergency department visits, and complication rates. While some patients may have received care outside our institution, our EMR system includes a comprehensive timeline feature that captures all hospital-based interactions. National systems in Saudi Arabia link all deaths to ID numbers and trigger automated EMR notifications to physicians when a registered patient dies, which supports the reliability of the mortality data.

Despite these limitations, our study offers novel and clinically relevant insights into pediatric PSH. It highlights key clinical patterns, diagnostic challenges, and therapeutic considerations and reinforces the urgent need for prospective, multicenter studies to refine diagnostic criteria and optimize management strategies for this complex and under-recognized condition.

Conclusion

In conclusion, PSH in pediatric patients predominantly arises from non-traumatic brain injuries, presenting with nonspecific symptoms that frequently lead to

misdiagnosis. Our study provides comprehensive insights into these clinical characteristics, diagnostic challenges, and management outcomes. We highlight the importance of early diagnosis and demonstrate clonidine's potential as a life-saving intervention. Furthermore, we emphasize the complementary role of non-pharmacological interventions such as environmental modifications, HBOT, and structured sensory stimulation. These combined therapeutic strategies have significant potential to enhance patient care, inform clinical guidelines, and guide future research toward refining diagnostic criteria and optimizing treatment strategies for pediatric PSH.

Abbreviations

PSH	Paroxysmal Sympathetic Hyperactivity
HIE	Hypoxic-Ischemic Encephalopathy
CBC	Complete Blood Count
ESR	Erythrocyte Sedimentation Rate
CRP	C-Reactive Protein
MRI	Magnetic Resonance Imaging
ECHO	Echocardiography
EEG	Electroencephalography
ICU	Intensive Care Unit
TBI	Traumatic Brain Injury
PSH	AM-Paroxysmal Sympathetic Hyperactivity Assessment Measure

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Author contributions
Wesam Althaqafi, MD, orchestrated the study as the principal investigator. She formulated the research team, conceptualized the study, supervised the initial proposal, and handled the submission and IRB approval processes. Dr. Althaqafi managed the distribution of case reviews among the researchers, led the data analysis, drafted and revised the manuscript, and ensured the acquisition of all necessary documentation such as bioethics certificates, GCP, and ORCID for team compliance.Waad Bader Almanie, MD, alongside Sulaiman Dakhel Almasoud, MD, undertook joint responsibilities for case review and data collection. Dr. Almanie was instrumental in creating the initial proposal, designing data collection methodologies, and overseeing the coding process. She diligently monitored the data analysis and collaborated closely with Dr. Althaqafi during regular progress reviews, playing a pivotal role in drafting the final manuscript.Duaa Baarmah, MD, enhanced the project by supervising its intellectual novelty and reviewing both the proposal and final manuscript. She enriched the study with her expert insights and contributed to determining suitable publication venues. Dr. Baarmah's overarching supervision ensured the study adhered to the highest academic standards.All contributions have been acknowledged, and each author has approved the final version of the manuscript, confirming their collaborative commitment to the study's integrity and its findings.

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Data availability
The datasets generated and analyzed during this study are not publicly available due to institutional restrictions on data sharing, as outlined in the Data Ownership Agreement established by KAIMRC. The data include de-identified clinical records, which cannot be openly shared to protect participant privacy. However, de-identified data may be made available from the corresponding author upon reasonable request and with explicit approval from KAIMRC. No secondary data were used in this study.

Declarations

Ethics approval and consent to participate
The Ethics Committee of King Abdullah International Medical Research Center (KAIMRC) reviewed and approved this study under approval NRC22R/096/02. The study was conducted as a retrospective chart review, utilizing existing de-identified data collected as part of routine care. This study did not involve any direct interactions with patients. Consequently, the Ethics Committee waived the need for informed consent, including from parents or legal guardians for participants under 16, following institutional guidelines and national regulations. All procedures complied with the ethical standards of KAIMRC and national ethical regulations. The authors acknowledged all contributions and approved the final version of the manuscript, confirming their joint commitment to the study's integrity and findings.

Consent for publication
Not applicable (No person's data in any form).

Competing interests
The authors declare no competing interests.

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