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CASE REPORT

Magnetic resonance imaging findings of bilateral thalamic involvement in severe paroxysmal sympathetic hyperactivity: a pediatric case series

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Abstract
Purpose Paroxysmal sympathetic hyperactivity is a complication of brain injury that has mainly been described in the adult brain injury literature.
Methods We present a case series of three pediatric patients that developed paroxysmal sympathetic hyperactivity of varying severity following hypoxic brain injury.
Results Comparison of brain magnetic resonance imaging revealed bilateral and symmetric global ischemic changes in all three cases. However, the thalamus was not affected in the patient with the mild case of paroxysmal sympathetic hyperactivity. In contrast, bilateral and symmetric damage to the thalamus was observed in the two severe cases.
Conclusions Our case series suggests that in hypoxic brain injury, evidence of bilateral ischemic injury to the thalamus on magnetic resonance imaging may be an important early predictor of severity and length of paroxysmal sympathetic hyperactivity. While this is an interesting observation, definite proof of our hypothesis requires further research including analysis of larger numbers of patients and comparison of MRI findings in children with hypoxic brain injury that do not develop paroxysmal sympathetic hyperactivity.

Keywords Dysautonomia · Paroxysmal sympathetic hyperactivity · Pediatrics · Acquired brain injury

Introduction

Paroxysmal sympathetic hyperactivity is a common complication of severe traumatic brain injury. It is a syndrome of intermittent agitation, diaphoresis, hyperthermia, hypertension, tachypnea, and extensor posturing [1–4]. In the adult patient population, paroxysmal sympathetic hyperactivity has been most commonly observed after severe traumatic brain injury, occurring in 7.7–33 % of cases [1]. It also occurs in a variety of other brain pathologies, including anoxic brain injury, brain tumors, hydrocephalus, and subarachnoid hemorrhage [3]. The symptoms can first present from 24 h to weeks following injury and may last for several months after [3]. The pathophysiology of paroxysmal sympathetic hyperactivity is not entirely clear. Overall, there is an increase in the activity of the sympathetic nervous system. This is thought to occur due to an imbalance of the sympathetic and parasympathetic nervous systems, caused by a disruption of cortical regulation, loss of autonomic balance control, or dysfunction of the hypothalamus and thalamus [2, 3].

In the pediatric patient population, relatively little is known about paroxysmal sympathetic hyperactivity [5]. The overall prevalence of paroxysmal sympathetic hyperactivity in children with acquired brain injury has been reported to be 13–14 % and most commonly observed following hypoxia-ischemia from cardiac arrest [5, 6].

This study was performed at the Alberta Children's Hospital, University of Calgary, Department of Clinical Neurosciences, Division of Physical Medicine & Rehabilitation and Department of Radiology.

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Outcomes in children with paroxysmal sympathetic hyperactivity are worse, with longer length of stays and lower pediatric functional independence measure scores on admission to rehabilitation [5]. We present a case series of three pediatric patients with paroxysmal sympathetic hyperactivity secondary to hypoxemic brain injury, focusing on our experience in clinical presentation and neuroimaging findings in this disorder.

Case description

Case 1

A previously healthy 8-year-old boy sustained a severe anoxic brain injury secondary to accidental strangulation. Two days post injury, magnetic resonance imaging revealed multifocal bilateral and symmetric areas of restricted diffusion including putamen, thalamus, and cerebral cortex in watershed regions of cerebral hemispheres (Fig. 1a–c; Table 1). Follow up imaging 21 days post injury revealed atrophy and hyperintense signal in bilateral caudate nuclei on fluid-attenuated inversion recovery images (Fig. 1d; Table 1).

Paroxysmal sympathetic hyperactivity episodes started 7 days post injury, with tachycardia (heart rate as high as 206), hypertension (systolic blood pressure as high as 174), tachypnea (respiratory rate as high as 36), diaphoresis, decorticate posturing, and dystonia. This patient had a severe course of paroxysmal sympathetic hyperactivity, lasting for 11 weeks and peaking in frequency and severity at 6 to 7 weeks. At the 6-week mark, the patient experienced four to six episodes per day, lasting minutes to hours. The episodes most often occurred in the evening and morning, although no specific trigger was identified. The patient was discharged home 4 months post injury, at which time his parents hired private rehabilitation therapists.

Case 2

An 8-year-old girl presented to the emergency department with acute onset of vomiting, headache, seizure, right-sided ptosis, and miosis. Shortly after presentation, her level of consciousness declined to Glasgow Coma Scale of 7. Urgent neuroimaging revealed a right frontal lobe mass, which proved to be a grade 3 anaplasic ependymoma. The patient was emergently taken to the operating room for a right frontotemporal craniotomy and tumor removal. She sustained a severe anoxic brain injury secondary to increased intracranial pressure. At 4 days post injury, magnetic resonance imaging showed multifocal bilateral and symmetric areas of restricted diffusion in putamen, caudate nucleus, cerebellar hemispheres, hippocampi, and cerebral cortex in watershed regions of cerebral hemispheres. The thalamus was not affected by the hypoxic brain injury, as demonstrated on initial and follow-up imaging (Fig. 1 panels 2-a, 2-b, 2-c, 2-d; Table 1).

Paroxysmal sympathetic hyperactivity episodes started at 4 days post injury. Overall, the severity and course was mild, lasting a total of 8 days. Symptoms included tachycardia (heart rate as high as 120), hypertension (blood pressure as high as 163/103), diaphoresis, dystonia, and posturing. Paroxysmal sympathetic hyperactivity episodes occurred up to four times per day, lasting seconds to minutes. She was discharged to a community-based rehabilitation program two and a half months post injury, having received intensive inpatient rehabilitation and several weeks of radiation therapy.

Case 3

A previously healthy 19-month-old boy sustained a severe hypoxic brain injury from respiratory arrest secondary to croup infection [7]. At 6 days post injury, magnetic resonance imaging showed extensive restricted diffusion in the cerebral hemispheres, with most striking changes in the cerebral white matter. Bilateral putamen, globi pallidi and caudate nuclei also showed restricted diffusion (Fig. 1, panels 3-a, 3-b and 3-c; Table 1). Follow-up imaging at 20 days post injury revealed symmetric atrophy and hyperintense signal in bilateral thalami on fluid-attenuated inversion recovery images (Fig. 1, panel 3-d; Table 1).

Eleven days post injury, he developed episodes of tachycardia (heart rate as high as 225), tachypnea (respiratory rate as high as 50), fever (temperature as high as 40 °Celsius), dystonia, and decerebrate posturing. He had a severe course of paroxysmal sympathetic hyperactivity, lasting a total of 7 weeks and peaking in frequency and intensity at 4 to 5 weeks. He was discharged from hospital 5 months post injury into a community-based rehabilitation program.

Discussion

Despite the similarities of the initial injuries, the course of paroxysmal sympathetic hyperactivity was quite different in our three cases. Two of the patients had a severe course, lasting much longer and had higher deviations in autonomic parameters. The third patient had a mild course, lasting for only 8 days with less severe symptoms. Differences in location and extent of brain damage may account for disparities observed in the clinical course. In our case series, comparison of brain magnetic resonance imaging reveals that the thalamus was not affected by hypoxic injury in our mild case of paroxysmal sympathetic hyperactivity. However, in both severe cases, hypoxic injury affected *bilateral* thalami. Interestingly, the thalamus may play an important role in autonomic control, as

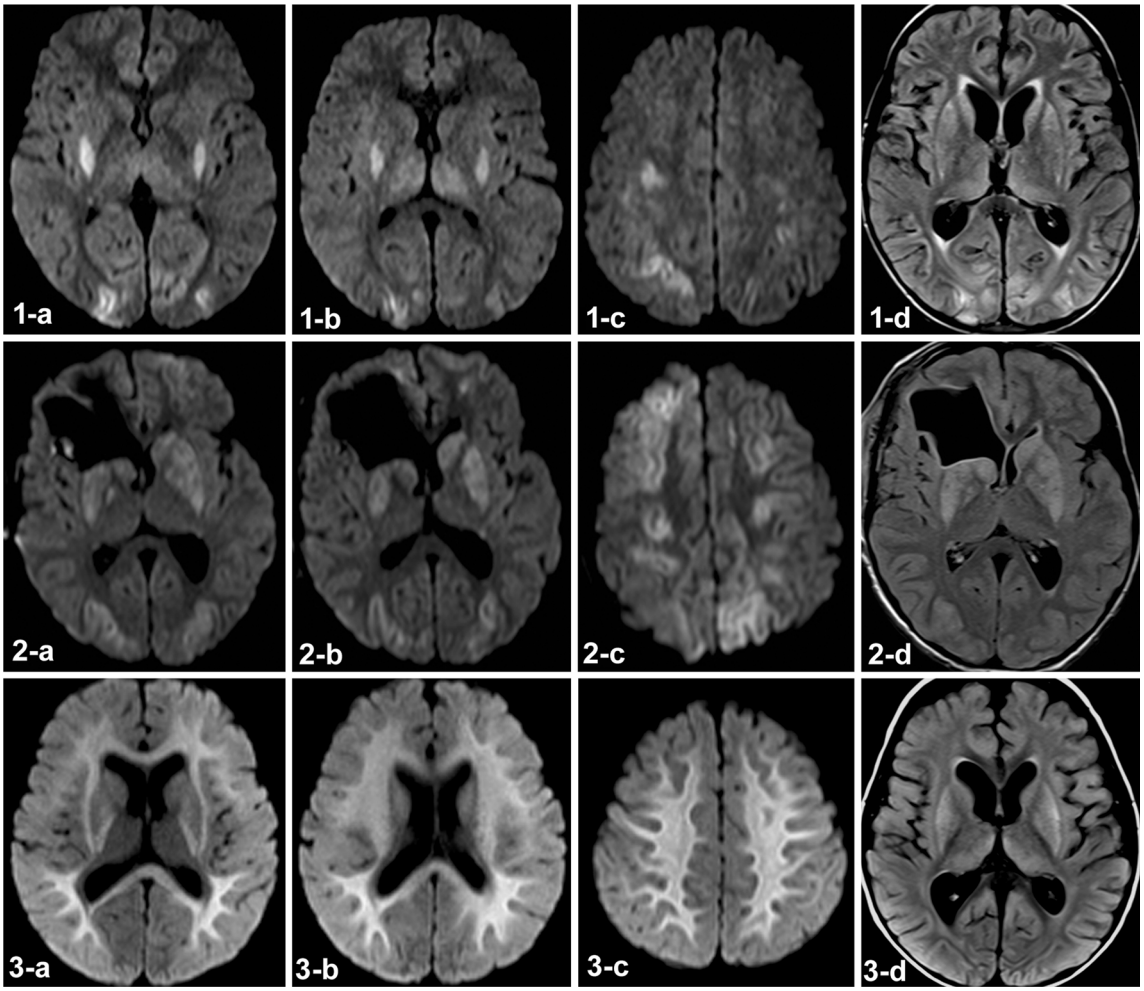

Fig. 1 Magnetic resonance imaging of all three patients. The images in the upper panel belong patient 1. On diffusion-weighted images obtained 2 days post-injury (1-**a**, 1-**b**, 1-**c**), hyperintense signal is seen in bilateral putamen, thalami, and watershed regions of cerebral hemispheres. Corresponding decreased signal is seen on apparent diffusion coefficient map (not shown). Follow up magnetic resonance imaging performed 19 days later revealed atrophy and hyperintense signal in bilateral caudate nuclei and atrophy on fluid-attenuated inversion recovery images (1-**d**). The images in the middle panel belong to patient 2. On diffusion-weighted images obtained 4 days post injury (2-**a**, 2-**b**, 2-**c**), restricted diffusion is seen in watershed regions of cerebral cortex, bilateral caudate nuclei, putamen, and globi pallidi. A large cavity is located in the right frontal lobe, which is secondary to pre-existing cystic neoplasm and surgery. Diffusion-weighted image changes were present on imaging performed prior to emergent tumor-resection surgery, but more prominent on this scan (2-**a**, 2-**b**, 2-**c**). On fluid-attenuated inversion recovery images obtained at 4 days post injury (2-**d**) and 60 days later (not shown), no abnormal signal is seen in the thalami. The images in the bottom belong to patient 3. On diffusion-weighted images of magnetic resonance imaging obtained 6 days post injury (3-**a**, 3-**b**, 3-**c**), extensive restricted diffusion is seen in cerebral white matter and cortical gray matter. Bilateral putamena, globi pallidi and caudate nuclei also have restricted diffusion. On fluid-attenuated inversion recovery images obtained 20 days post injury (3-**d**), atrophy and hyperintense signal in caudate nuclei and thalami are noted

suggested by studies on fatal familial insomnia as well as animal studies [8–10]. Fatal familial insomnia is a hereditary prion disease that is pathologically characterized by severe degeneration of *bilateral* mediodorsal and anterior thalamic nuclei, with sparing of other autonomic centers, including hypothalamus and brainstem [8, 9]. Clinical manifestations of fatal familial insomnia include progressive dysautonomia (tachycardia, hypertension, hyperhidrosis, and hyperthermia), insomnia, motor dysfunction, and circadian abnormalities. It is interesting to note the similarities in symptoms as well localization of brain damage to *bilateral* thalami for fatal familial insomnia patients and our cases of severe paroxysmal sympathetic hyperactivity.

One previous study has investigated magnetic resonance imaging findings in adults with paroxysmal sympathetic hyperactivity following severe traumatic brain injury [11]. Damage to the deep gray matter structures were reported in 56 % of patients who developed paroxysmal sympathetic hyperactivity and 25 % of patients

Table 1 Location of ischemic damage on initial and follow up brain magnetic resonance imaging. The date of the initial and follow up magnetic resonance imaging is indicated as days post injury. Ischemic damage to specific regions is denoted with "x". All of the lesions were bilateral and symmetric. Thalamic involvement is highlighted for each case

	Case 1		Case 2		Case 3	
Location of lesions*	*2 days*	*21 days*	*4 days*	*60 days*	*6 days*	*20 days*
Cortex and subcortical white matter	x	x	x	x	x	x
Periventricular white matter					x	x
Corpus callosum					x	
Thalamus	x	x				x
Caudate		x	x	x	x	x
Globus pallidus			x	x	x	x
Putamen	x	x	x	x	x	x
Brainstem						

* all lesions were bilateral and symmetric

without paroxysmal sympathetic hyperactivity [11]. This result suggests that injury to brain structures other than the thalamus may lead to paroxysmal sympathetic hyperactivity and that damage to thalamus may also be observed in patients without paroxysmal sympathetic hyperactivity. However, it is unclear whether the reported damage involved unilateral or bilateral brain structures. With traumatic brain injury, one may expect more asymmetric involvement compared to anoxic brain injury. In the pathophysiology of severe paroxysmal sympathetic hyperactivity, damage to *bilateral* thalami may be required for symptom development, as seen in our case series as well as fatal familial insomnia. Clinically, it would be very useful to predict more severe cases of paroxysmal sympathetic hyperactivity in earlier stages of recovery from brain injury. This would allow the clinician to decide the best location and level of monitoring for the patient, as well as anticipate medical complications and plan for more extensive treatment options. Furthermore, if future studies prove that thalamic involvement is an important determinant of paroxysmal sympathetic hyperactivity severity, this may lead to development of more effective medical and/or interventional treatment options.

Our study has several limitations, including the small sample size and lack of a true negative control—analysis of MRI findings of children with hypoxemic injury that do not develop paroxysmal sympathetic hyperactivity. Furthermore, in case 2, it is unclear whether surgery itself may have affected clinical outcomes. As such, we present an interesting observation and hypothesis, linking MRI findings of bilateral thalamic ischemic damage and clinical manifestation of severe paroxysmal sympathetic hyperactivity. Definitive proof of this correlation will require future studies of larger cohorts and comparison of MRI findings in children with hypoxic brain injury that do not develop paroxysmal sympathetic hyperactivity.

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Author contributions Serge Mrkobrada wrote the manuscript, cared for the patient in case 3, analyzed the clinical/radiological data, and made Table 1.

Xing-Chang Wei analyzed and acquired the radiological data, critically revised the manuscript, and made Fig. 1 and Table 1.

Vithya Gnanakumar cared for all of the patients, critically revised the manuscript, and analyzed the clinical data.

Compliance with Ethical Standards

Conflict of interest The authors have no conflicts of interest to declare.

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Ethical approval We have obtained written permission from the patients' parents to write this case series.

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