

# Baroreflex Failure, Sympathetic Storm, and Cerebral Vasospasm in Fibulin-4 Cutis Laxa

## abstract

Sudden, severe, and life-threatening, the crises associated with baroreflex failure are diagnostically challenging, particularly in children, a population in which it has rarely been described. The baroreflex failure syndrome results from impaired afferent baroreceptive input and manifests with autonomic stimulation-induced surges in blood pressure and heart rate accompanied by distinct signs, including thunderclap headache, diaphoresis, and emotional instability. Although the adult literature includes cases of severe headache in baroreflex failure,<sup>1,2</sup> we present the first case of a child with recurrent thunderclap headache and cerebral vasospasm with baroreflex failure secondary to vascular complications of a rare genetic connective tissue disorder. *Pediatrics* 2014;133:e1396–e1400

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### KEY WORDS

baroreflex, intracranial vasospasm, cutis laxa, thunderclap headache, child

### ABBREVIATIONS

BFS—baroreflex failure syndrome  
BP—blood pressure  
CT—computed tomography  
HR—heart rate  
RCVS—reversible cerebral vasoconstriction syndrome

Dr Rajapakse drafted the initial manuscript and reviewed and revised the manuscript per coauthor suggestions; Drs Mineyko and Chee drafted a portion of the initial manuscript and reviewed the manuscript; Dr Subramaniam provided expertise in neurology for case diagnosis and history analysis and critically reviewed the manuscript; Dr Dicke provided expertise in pediatric cardiology for case history analysis and critically reviewed the manuscript; Dr Bernier provided expertise in medical genetics for case history analysis and critically reviewed the manuscript; Dr Kirton provided expertise in pediatric stroke neurology for case history analysis and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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Sudden, severe, and life-threatening, baroreflex failure crises are diagnostically challenging, particularly in children, a population in which they are rarely described. Baroreflex failure syndrome (BFS) results from impaired afferent baroreceptive input and manifests with autonomic stimulation–induced surges in blood pressure (BP) and heart rate (HR) accompanied by distinct signs, including thunderclap headache, diaphoresis, and emotional instability.<sup>1,2</sup> We describe a child with recurrent thunderclap headache and cerebral vasospasm with BFS secondary to vascular complications of cutis laxa.

### CASE HISTORY

A 7-year-old boy was thrown backward off the shoulders of a playmate into 2 feet of cold lake water. His head was submerged, but did not impact the bottom. He instantaneously experienced the most severe headache of his life. The pain was extreme, holocephalic, and resulted in marked distress. His symptoms abated over 1 to 2 hours, and he returned to normal. He was reviewed at a primary care facility and discharged despite a unique medical history. Paroxysmal recurrences of the same events occurred over the following 72 hours. Some were spontaneous, including awakening him from sleep; another was precipitated by diving into a swimming pool. All resolved over hours with no neurologic symptoms except marked distress and panic. On presentation to the emergency department with symptoms resolving, he was hypertensive (systolic BP 140 mm Hg) but otherwise normal. He was admitted.

The patient had a personal and family history of a rare connective tissue disorder known as autosomal recessive cutis laxa, subsequently determined to be secondary to a fibulin-4 mutation (ARCL1B).<sup>3</sup> This disorder is character-

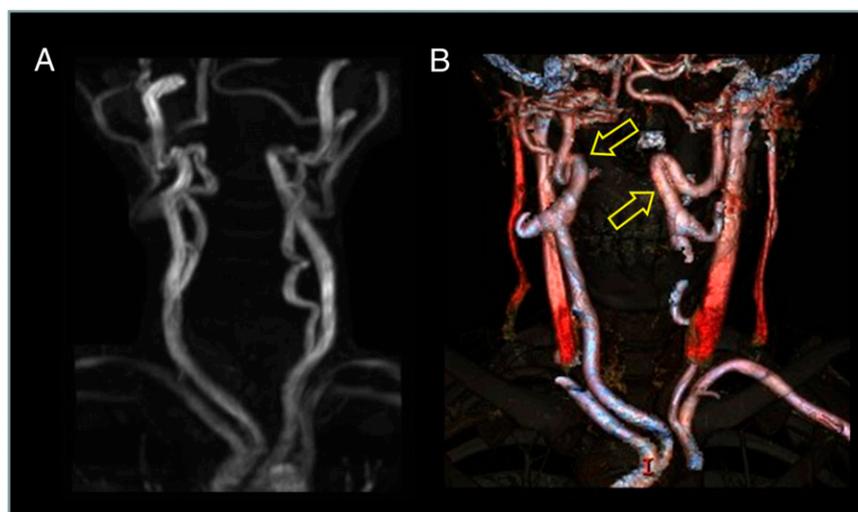
ized by skin laxity, arterial tortuosity and aortic aneurysms, emphysema, and features of connective tissue disorders such as hypermobility and inguinal hernias.<sup>3</sup> He was followed for aortic root dilatation with mechanical aortic valve replacement at 22 months. He was anticoagulated with warfarin and afterload reduced with enalapril. He had had monthly headaches since 2 years of age that met criteria for migraine with aura. Attacks were severe, usually waking him from sleep, and were relieved by vomiting.

Magnetic resonance imaging was normal except for marked craniocervical arterial tortuosity (Fig 1). Abortive acetaminophen was effective, but prophylaxis with riboflavin did not improve headache frequency. Nine months before presentation, he began experiencing unexplained, unprecipitated presyncope lasting minutes that was now occurring daily. Development was normal.

Family history included 3 second-degree relatives with fatal aortic dissections in infancy and others with migraine.

After admission, the paroxysmal events of thunderclap headache, hypertension, and diaphoresis continued several times per day. Some were associated with stress such as emotional upset or needing to urinate. BPs remained elevated and fluctuated dramatically, ranging from systolic 110 mm Hg (HR 50) while settled and asymptomatic to systolic >200 mm Hg (HR 110–120) during the episodes. Extreme distress during events converted to entirely normal within minutes between them. Oral nifedipine was titrated without consistent effect.

Pediatric neurology was consulted and witnessed a typical episode. An unprecipitated, rapid increase in HR (>100) and BP (>160 systolic) occurred over 1 to 2 minutes. The boy became extremely flushed and diaphoretic. He was able to complete a full neurologic examination but was markedly distressed, repeatedly uttering, “My head, my head! I’m dead, I’m dead.” He later confirmed he was experiencing a strong sense of “impending doom” when the term was explained to him.



**FIGURE 1**

Arterial tortuosity. A, Cervical magnetic resonance angiogram from January 2011 demonstrates tortuosity of all cervical vessels. B, CT angiogram performed on presenting admission demonstrates the same. Marked folding of both internal carotid arteries onto themselves is noted in the neck in the region of the baroreceptors (arrows). Although the imaging methods and head position may be different, there is a suggestion that this “kinking” is worse than it was on the original scan 7 months earlier.

Episodes continued to occur 2 to 3 times per day, lasting 20 to 60 minutes, then abruptly returning to normal. He was transferred to intensive care for arterial line insertion, continuous BP monitoring, and management of hypertension and pain. With continuous BP monitoring, events became predictable, as BP would increase over 5 to 20 minutes with symptoms beginning at ~130 mm Hg. Nitroprusside and esmolol infusions could not produce sustained BP control or alter event frequency. Morphine infusion was required for pain. Interictal examinations remained normal aside from a murmur. Visible pulsatile neck masses were subsequently noted (Fig 2).

Computed tomography (CT) of the head was normal. Because of anticoagulation, stress effects, and subsequent investigations, lumbar puncture was deferred. CT angiogram of the head and neck excluded dissection or aneurysm but confirmed multifocal areas of smooth, “sausage-like” narrowing of midsized cerebral arteries consistent with vasospasm (Fig 3). CT angiogram also demonstrated marked carotid tortuosity with redundant sections “folding back” on themselves bilaterally (Fig 1). Routine studies, urine catecholamines, and abdominal/renal ultrasounds were normal. Electrocardiogram and echocardiogram were unchanged.

The patient met criteria for reversible cerebral vasoconstriction syndrome (RCVS; previously known as Call-Fleming syndrome). A connection to his chronic headaches, Presyncope, and cutis laxa was suspected. The bilateral carotid “folding” was hypothesized to be distorting BP sampling by carotid body afferents. Combined with his clinical syndrome of thunderclap headache, vasospasm, malignant hypertension, and dysautonomia, this suggested BFS. He was therefore started on clonidine ( $\alpha$ -2 agonist) to target

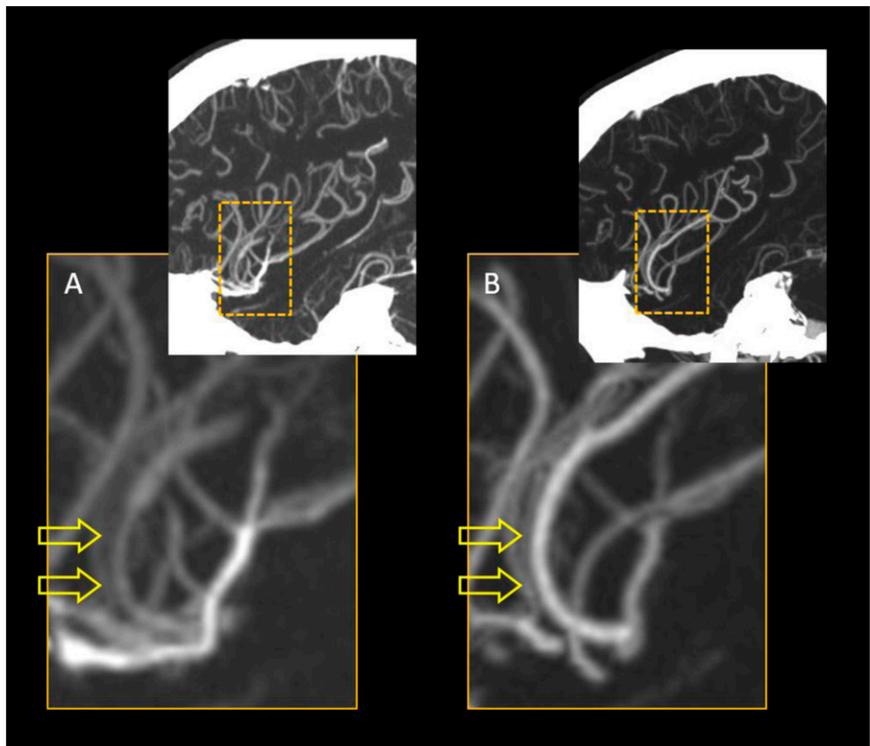


**FIGURE 2**

Pulsatile neck masses: prominent, visibly pulsatile masses were evident in the neck bilaterally.

sympathetic overactivity. Clonazepam, child psychology, and environmental modulation were also used to reduce anxiety. Titration of clonidine to

8 mg/kg/d over 3 days saw his crises steadily decrease with normalization of BP. He was discharged entirely well 2 days later on clonidine 50 mcg 4 times



**FIGURE 3**

Cerebral vasospasm. A, CT angiogram at presentation demonstrates smooth, concentric, “sausage-like” narrowing (arrows) at 1 of several medium-sized cerebral arteries bilaterally consistent with vasospasm. B, Repeat CT angiogram at same location 15 weeks later shows complete resolution with robust flow through the same arterial segment (arrows).

daily and clonazepam 50 mcg 3 times daily. At 3 months, the patient was essentially normal. A clonidine patch was tried for dosing convenience, but oral 3 times daily (50/50/75 mg) dosing was resumed because of skin irritation. He had occasional morning migraines consistent with previous episodes. BPs were normal on ambulatory monitoring, and his presyncopal symptoms resolved completely. He returned to all normal activities. Follow-up imaging confirmed resolution of vasospasm (Fig 2). Seven months later, his clonidine was discontinued before scheduled aortic valve replacement. Postoperatively, he experienced critical, refractory hypertension that resolved when clonidine was resumed. At 18 months, he is normotensive with resolution of his secondary vascular headaches and new symptoms of Raynaud phenomenon. His hobbies include swimming, and he can dive 10 m without difficulty.

## DISCUSSION

BFS secondary to genetic connective tissue disorder has not been described. Rarely reported in children, recognition of this paroxysmal dysautonomia was possibly lifesaving, particularly given his anticoagulation and fragile aortic arch.

Baroreflexes buffer changes in arterial pressure to maintain homeostasis.<sup>4</sup> The arterial baroreflex originates from stretch-sensitive receptors in the carotid sinus wall, aortic arch, and large thoracic vessels. Afferent fibers join the glossopharyngeal nerve and project to the nucleus tractus solitarius and other cardiovascular nuclei in the medulla. The efferent limb consists of sympathetic and parasympathetic fibers to the heart and blood vessels.<sup>5</sup> Adult causes of BFS are many but typically involve disruption of bilateral baroreflex afferents<sup>6</sup> (Table 1). Combining this neuroanatomy with clinical

recognition of BFS should inform lesion localization.

The clinical presentation of baroreflex failure is distinct. The differential diagnosis includes pheochromocytoma, which requires exclusion. The differential of thunderclap headache is also broad (Table 2), and it is imperative to rule out subarachnoid hemorrhage and arterial dissection, particularly with anticoagulation or connective tissue disorder. Similar triggers to those seen in our patient can also trigger thunderclap headache in adults, including bathing in cold or hot water, emotion, and urination. Thunderclap headache in RCVS has also been described with autonomic dysreflexia in an adult with neurogenic bladder after traumatic spinal cord injury.<sup>7</sup>

We propose the pathogenic mechanism of BFS here was progressive infolding of bilateral carotid arteries, impairing baroreceptor pressure sampling. This chronic process would also explain the previous symptoms of worsening presyncope and unusual acute vascular headaches, which both resolved within months of clonidine treatment.

Our patient had clinical features (multiple thunderclap headaches) and angiographic criteria fully consistent with RCVS, which is rarely reported in children.<sup>8,9</sup> Relevant to BFS, other “sympathomimetic” triggers of RCVS are well described in adults, including medications, illicit drugs, and pheochromocytoma.<sup>10</sup> Diving has also been

**TABLE 1** Causes of Baroreflex Failure<sup>6</sup>

Trauma
Surgery (carotid endarterectomy, carotid body tumor resection)
Brainstem stroke
Tumor growth, paragangliomata
Irradiation
Leigh syndrome
Afferent sensory neuropathy
Genetic (Groll-Hirschowitz syndrome, hypertension-brachydactyly syndrome, arterial tortuosity syndrome <sup>a</sup> )

<sup>a</sup> Fibulin-4 mutation, patient discussed in this report.

**TABLE 2** Causes of Thunderclap Headache<sup>12,13</sup>

Hemorrhage (subarachnoid, intracerebral, intraventricular)
RCVS
Sentinel headache
Cerebral venous sinus thrombosis
Cervical artery dissection
Spontaneous intracranial hypotension
Pituitary apoplexy
Retroclival hematoma
Ischemic stroke
Acute hypertensive crisis
Posterior reversible encephalopathy syndrome
Third ventricle colloid cyst
Tumor
Intracranial infection
Primary thunderclap headache
Primary cough, sexual, and exertional headache

described as a precipitant in 1 of the few pediatric cases of RCVS.<sup>8</sup> Our case suggests that BFS should be added to the differential for thunderclap headache in children, and appropriate cerebrovascular imaging can be used to document and follow cerebral vasospasm.

Altered HR responses to nitroprusside or phenylephrine may be diagnostic in BFS.<sup>11</sup> The cold pressor test may also cause marked BP increases in BFS.<sup>4,11</sup> We were unable to systematically perform such testing in our patient because of his clinical instability. Other precipitants included both mental and physical stressors, suggesting these are also important management targets in children. Precipitation of 2 events by head submersion is likely explained by the sympathetic surge of the human diving reflex.

Typical of BFS was a dramatic response to clonidine.<sup>4,11</sup> Clonidine, a presynaptic  $\alpha_2$ -agonist inhibiting sympathetic transmitter release, can reduce the frequency and magnitude of hypertensive surges by reducing central and peripheral sympathetic activation.<sup>11</sup> Although our patient incurred skin toxicity, patients may prefer patch formulations to inconvenient oral 3 times or 4 times daily dosing.<sup>6</sup> An alternative  $\alpha$ -blocker is phenoxybenzamine.<sup>4</sup> BFS

may also respond to benzodiazepines, possibly related to anxiolytic properties or tonic  $\gamma$ -amino-butyric acid–ergic control of sympathoexcitatory neurons in the rostral ventrolateral medulla.<sup>1</sup> Additional BFS management based on limited evidence includes hemodynamic monitoring in intensive care and prevention of severe hypertension complications.

The natural history of adult BFS suggests that some patients can eventually be weaned off clonidine after stability over years.<sup>4</sup> This may represent a “resetting” of central control systems, similar to that seen after vestibular injury, but the pathophysiology is not understood. This will necessitate future reevaluations, although the dramatic effects of cloni-

dine discontinuation suggest that his current need is great.

This case highlights the recognition of a distinct, life-threatening, treatable neuroautonomic syndrome and the importance of considering fundamental anatomy and physiology to elucidate pathophysiology and guide management.

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