


# Metabolic Strokes in Propionic Acidemia: Transient Hemiplegic Events Without Encephalopathy

Child Neurology Open  
Volume 6: 1-9  
© The Author(s) 2019  
Article reuse guidelines:  
sagepub.com/journals-permissions  
DOI: 10.1177/2329048X19873242  
journals.sagepub.com/home/cno  


Mohammed Almuqbil, MD, FRCPC<sup>1,2,3</sup>, Jeffrey M. Chinsky, MD, PhD<sup>1,4</sup>,  
and Siddharth Srivastava, MD<sup>5</sup> 

## Abstract

Metabolic strokes are a notable feature associated with acute catabolic crises in patients with propionic acidemia. Despite their importance, these events are not well characterized. Here, we present the clinical history of a patient with propionic acidemia who developed 5 episodes of acute hemiparesis between 3 and 11 years of age. The clinical finding of hemiparesis associated with 4 of these 5 events were shorted lived (2-5 days). Neuroimaging showed signal changes in the basal ganglia manifesting many years following the initial episode. Two of the episodes were accompanied by definite seizures. Based on these factors, the hemiparetic events were most consistent with metabolic strokes, though what is distinctive is that most of the events occurred without evidence of metabolic decompensation; brain magnetic resonance imaging findings were not suggestive in the acute setting. We present a framework for evaluating suspected metabolic stroke in propionic acidemia, in light of the sometimes perplexing clinical heterogeneity underlining these events.

## Keywords

propionic acidemia, metabolic strokes, hemiparesis, hemiplegia

Received April 2, 2019. Received revised June 2, 2019. Accepted for publication July 14, 2019.

Metabolic strokes, defined as neurological deficits due to biochemical disturbances in focal brain regions not attributable to ischemic or hemorrhagic causes,<sup>1</sup> are one of the distinct manifestations of acute catabolic crises in a number of mitochondrial and metabolic disorders, especially those affecting amino acid catabolism.<sup>2</sup> One of the conditions associated with these presentations is propionic acidemia (OMIM: #606054), a disorder of branched chain amino acid metabolism caused by deficient activity of propionyl CoA carboxylase (EC 6.4.1.3).<sup>3</sup> Classically, this disorder presents with metabolic acidosis, hyperammonemia, and progressive encephalopathy, usually responsive to intensive medical management to reverse the catabolic crisis. Affected individuals may demonstrate a wide range of symptoms at any time throughout their lives but especially during the newborn period to late infancy/early childhood.<sup>4</sup>

In propionic acidemia, injury to the central nervous system can cause a wide range of neurological problems,<sup>5</sup> but what differentiates metabolic strokes from these other presentations is their tendency to cause neurological symptoms that are more focal or severe than typically expected of propionic acidemia

crises. Although the ongoing symptoms can be variable in length and are often reversible with appropriate treatment of metabolic abnormalities, there is strong evidence they are associated with negative long-term developmental outcomes.<sup>5,6</sup> In general, the neurologic manifestations of metabolic strokes can be quite severe, ranging from varying degrees of mental status change to complete neurological collapse, with or without

<sup>1</sup> Institute of Genetic Medicine, Johns Hopkins Hospital, Baltimore, MD, USA

<sup>2</sup> Division of Pediatric Neurology, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

<sup>3</sup> King Abdullah International Medical Research Center, King Abdullah Specialist Children's Hospital—Ministry of National Guard, Riyadh, Saudi Arabia

<sup>4</sup> Department of Pediatrics, Johns Hopkins Hospital, Baltimore, MD, USA

<sup>5</sup> Department of Neurology, Boston Children's Hospital, Boston, MA, USA

## Corresponding Author:

Siddharth Srivastava, Department of Neurology, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, USA.

Email: siddharth.srivastava@childrens.harvard.edu



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<http://www.creativecommons.org/licenses/by-nc/4.0/>) which permits any use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

superimposed focal deficits. In addition, there is usually laboratory evidence of metabolic decompensation occurring at the same time as, or immediately prior to, symptom presentation. In some cases, during periods of biochemical derangements, affected individuals demonstrate hemiparesis/hemiplegia that may persist to varying degrees. In these instances, there may not be imaging finding in the brain to suggest acute hemorrhage or ischemia.

In this report, we present a case of a child with propionic acidemia who presented with recurrent episodes of acute marked hemiparesis concerning for metabolic stroke. Many of these events were not accompanied by biochemical evidence of metabolic decompensation nor any sign of metabolic encephalopathy in 3 of the events. In 4 of the 5 events, associated neurologic deficits resolved within 2 to 5 days. Moreover, brain magnetic resonance imaging (MRI) findings were not suggestive of a diagnosis in the acute setting. In light of the sometimes perplexing clinical heterogeneity underlining similar events described in the literature surrounding metabolic strokes in propionic acidemia and our patient, we suggest a framework for evaluating suspected metabolic stroke in propionic acidemia.

## Case

The patient is a recently deceased 22-year-old male diagnosed with propionic acidemia during his first week of life. He was born at full-term gestation via cesarean delivery secondary to breech presentation. Following an unremarkable 2-day course in which he was breastfed, on day of life 3, he developed symptoms of poor feeding that progressed to hypothermia, hypoglycemia, and marked hypotonia. His laboratory work revealed mild metabolic acidosis (serum bicarbonate 15 mEq/L), mild hyperammonemia (83  $\mu\text{mol/L}$ ), marked ketonuria, very low carnitine levels, and a urine organic acid pattern consistent with propionic acidemia. He was started on a protein-restricted diet and carnitine therapy during days of life 3 to 5, and his diagnosis was confirmed by absent propionyl CoA carboxylase activity in white blood cell pellet extracts, with no response to biotin (laboratory of Bruce Barshop, MD, PhD, University of California San Diego, personal communication, 1995).

Despite ongoing appropriate treatment since that time, he had several episodes of metabolic decompensation during childhood. He had 4 significant hyperammonemic episodes (ammonia between 150 and 200  $\mu\text{mol/L}$ ) associated with metabolic ketoacidosis (pH 6.9-7.0) during his first 3 years of life. Over the next year, he was hospitalized 4 to 6 times due to ketoacidosis crises. These events were associated with hyperammonemia and acidosis, often following a prodromal viral infection, and they responded to intravenously (IV) fluids (D10  $\frac{1}{4}$  normal saline (NS) or  $\frac{1}{2}$  NS at twice daily maintenance rate) and IV carnitine (25-50 mg/kg IV every 6 hours).

The first episode that raised the possibility of a metabolic stroke occurred when he was 3.5 years old (see Table 1). He presented with severe ketoacidosis (venous pH 7.21, bicarbonate 8 mEq/L) and normal initial ammonia (25  $\mu\text{mol/L}$ ), and he was treated with IV dextrose electrolyte fluids and carnitine as

stated previously. However, although his metabolic derangements were improving over a 12-hour period, he demonstrated 4 brief (60-100 seconds each) focal to bilateral tonic-clonic seizures whose semiology included rightward eye deviation and prolonged (2 minutes) right arm jerking during the fourth spell. At that time, venous pH was 7.23 and measured bicarbonate was 11 mEq/L, though these values had been improving until that point. Notably, ammonia was minimally elevated (82  $\mu\text{mol/L}$ , maximum during the episode).

He became apneic requiring intubation and remained comatose for 3 days followed by 3 months of inpatient hospitalization and inpatient rehabilitation. Afterward, he demonstrated 9 months of severe choreoathetosis with left- greater than right-sided weakness. He clinically recovered completely, but only after 9 months. Notably, however, multiple head computed tomographies (CTs), MRIs, and electroencephalographies (EEGs) during this time showed no abnormalities to explain his presentation and initial course.

Subsequently, he had 4 more episodes concerning for metabolic stroke, between the ages of 6 and 11 years (see Table 1). All of them were associated with acute onset of marked right-sided hemiparesis (involving his right upper and lower extremity and occasionally his face), with or without seizures or encephalopathy, with near-complete resolution within 2 to 5 days. Two of the episodes were associated with infectious prodromal symptoms during the week prior to presentation. However, 3 of the 4 episodes, at ages 6, 9.8, and 10.5 years, were not associated with encephalopathy or seizures.

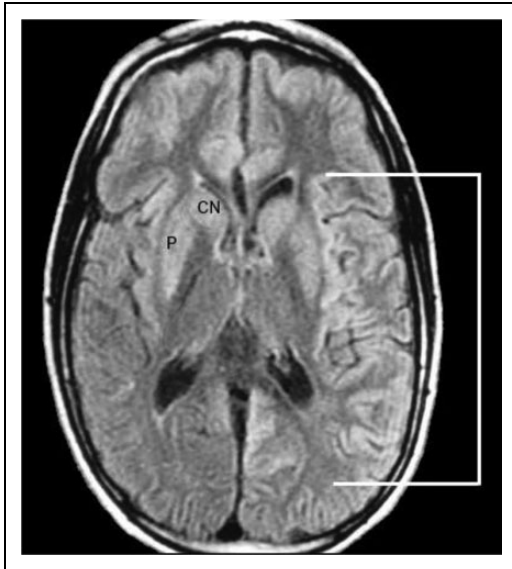
Neuroimaging findings were mixed. Brain MRI during one of the episodes when he was 6 years old showed involvement of the basal ganglia with increased T2 fluid-attenuated inversion recovery signal in the caudate and putamen, in addition to hyperintensities in the cortex and subcortical white matter (see Figure 1). Brain MRI during the episode at 7.5 years of age showed findings of subtle hyperintensity in the left frontal lobe, parietal lobe, insular cortex, and singular gyrus. Head CT or brain MRI during the other episodes did not show findings related to the acute presentation. Of note, none of these episodes was associated with significant hyperammonemia and only one, the first episode, exhibited significant ketoacidosis. Occasionally, mild ketoacidosis was observed on the second day (eg, at age 6 years, he exhibited a bicarbonate of 22 with an ammonia of 46  $\mu\text{mol/L}$  on presentation, but on the next day, he demonstrated a bicarbonate of 15 mEq/L with an ammonia of 76  $\mu\text{mol/L}$  which on repeat was 36  $\mu\text{mol/L}$ ). During the clinical presentation at 7.5 years of age, initially the patient had no evidence of metabolic decompensation based on serum biochemistry (ammonia 35  $\mu\text{mol/L}$ , bicarbonate 20 mEq/L, pH 7.4), but his cerebrospinal fluid lactate was elevated (5.22 mmol/L). Of note, his plasma amino acids were normal during that time.

In all cases except the first, there was improvement in the initial marked hemiparesis by discharge, with complete resolution in 2 to 5 days. Long-term apparent sequelae included intellectual disability (scattered developmental abilities at the 18- to 36-month-old level at 18 years of age), cortical visual

**Table 1.** Clinical Summary of Each Episode of Suspected Metabolic Stroke in the Patient.

Age	Clinical Presentation	Additional Examination Findings	Evidence of Significant Metabolic Decompensation			Head CT Findings	Brain MRI Findings	Initial Treatment	Discharge Examination	Total Resolution
			Plasma	CSF	EEG Findings					
3.5 years	Lethargy 4 brief Sz Coma		Yes (severe KA, mild HA)	NP	Generalized slowing, L > R L-sided focal sharp waves	Prominent sulcal pattern, L > R Poorer gray/white matter differentiation on the R	Mild diffuse atrophy Overall delayed myelination pattern	IV carnitine D10W-containing IVF	Severe choreoathetosis L > R weakness	9 months
6 years	RUE, RLE hemiparesis		Not on presentation but mild acidosis on next day	NP	NP	NP	Subtle hyperintensity in B/L caudate and putamen Hyperintensity in cortex and subcortical white matter with swelling involving L frontal lobe	IV carnitine D10W-containing IVF	Improvement in R hemiparesis	3 days
7.5 years	3 days of rhinorrhea, concern for viral sinusitis Lethargy GTC sz after admission RUE, RLE hemiparesis	L-ward eye deviation B/L LE hyperreflexia R ankle clonus	No	Yes	L-sided focal slowing	NP	Subtle hyperintensity in L frontal lobe, parietal lobe, insular cortex, and cingulate gyrus	Phenytoin load and initiation of carbamazepine IV carnitine D10W-containing IVF	Normalization of tendon reflexes Persistent R-sided hemiparesis (leg affected more than arm) but improvement in strength to 2-3/5 in 48 hours	5 days
9.8 years	RUE, RLE hemiparesis 4- to 5-day history of fever, cough, congestion RUE, RLE hemiparesis		No	NP	Dilatation of the sulci and cisterna magna L maxillary and L ethmoid sinusitis	NP		PO carnitine (IV unable to be placed) Protein restricted formula	Spontaneous movements of RUE ↓ but improved movement of RLE	3-4 days
10.5 years	Possible sz (2 drop spells) R facial droop RUE, RLE hemiparesis	B/L hypertonia R ankle clonus	No	NP	Generalized slowing R frontal epileptiform discharges	Cortical atrophy	Diffuse cortical atrophy R parietal and occipital cortex shows slight FLAIR hypointensity No signal abnormality on diffusion-weighted images; normal MRA	IV carnitine D10W-containing IVF Protein restricted formula	Spontaneous movements of RUE ↓ but improved movement of RLE Minimal R ankle clonus	2-3 days

Abbreviations: B/L, bilateral; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalography; FLAIR, fluid-attenuated inversion recovery; GTC, generalized tonic clonic; HA, hyperammonemia; IV, intravenous; IVF, intravenous fluids; KA, ketoacidosis; L, left; LE, lower extremity; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NP, not performed; R, right; RLE, right lower extremity; RUE, right upper extremity; sz, seizure; ↓, decreased.



**Figure 1.** Representative image from axial T2 fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) of the patient at 6 years of age. The image is notable for hyperintensities in the bilateral caudate nucleus (indicated by “CN”) and bilateral putamen (indicated by “P”) as well as left cortex and subcortex (indicated by the bracket).

and auditory impairment, generalized mild hypertonicity, intermittent intention tremors, and mild ataxia. During the second decade of life, he presented with fewer episodes of typical but mild propionic ketoacidemic crises, always associated with concomitant common infection (influenza, sinusitis, viral pneumonia); during some years, there were 2 to 3 hospitalizations, while during others, there were one or none. None of these episodes had evidence of hemiplegia on physical examination. The patient ultimately died at 22 years of age from an unexpected prolonged arrhythmic event in the absence of any clinical or biochemical findings for a preceding or concurrent typical propionic ketoacidemic decompensation.

## Discussion

Metabolic strokes play an important role in the natural history of propionic acidemia, yet they often present with a confusing range of signs and symptoms, as evident by our patient. The definition of this clinical entity needs to be clarified because it is not merely the presence of a focal deficit or neurological collapse in the context of metabolic derangement. At times, there are no imaging correlates with metabolic strokes, in contrast to vascular strokes, and there may not be associated biochemical changes. Although metabolic stroke has been reported more commonly in methylmalonic academia compared to propionic acidemia, stroke-like episodes in patients with propionic acidemia are increasingly recognized.<sup>7</sup>

Not surprisingly, it is often necessary to exclude other causes before making a diagnosis. This patient with propionic acidemia developed 5 episodes of acute hemiparesis (4 of which affected his right side) concerning for metabolic strokes

between the ages of 3 and 11 years. All of the events were transient in nature, with symptoms lasting between 2 and 5 days in 4 of the 5 episodes, suggesting that a permanent process was not in effect. Neuroimaging (either MRI or CT of the brain) did not reveal any evidence of an acute vascular stroke. Bilateral signal changes in the caudate and putamen, which may be the consequences of metabolic compromise, ultimately manifested many years following the initial severe metabolic stroke-like episode at 3.5 years of age, similar to those observed in earlier reported studies.<sup>5,8</sup> These neuroimaging changes did not seem to correspond with the physical examination findings of unilateral hemiparesis. There was no history of other symptoms to suggest migraines. During the rapidly transient episodes, the patient was alert and interactive, trying to voluntarily overcome the hemiparesis in attempted ambulation and directed tasks. Two of the episodes were accompanied by definite seizures, which can occur alongside metabolic strokes, complicating the diagnosis. However, on other occasions, EEGs did not suggest epileptic changes. After excluding other causes (including transient ischemic attack, vascular infarction, migraine, and Todd paresis) and recognizing the occasional clinical contributions of other conditions (seizures), the best explanation for this patient’s presentations of acute but reversible hemiparesis is metabolic stroke.

Metabolic strokes occur in a number of metabolic and mitochondrial disorders. The prototypical model for metabolic strokes is mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome, with prevalence rates of metabolic strokes as high as 60%. The cerebral disturbance in MELAS syndrome commonly results from mitochondrial dysfunction in those brain regions. Confounding this clinical picture is the fact that patients with MELAS syndrome may have neuroimaging findings that can also be seen in vascular stroke.<sup>1</sup> Apart from mitochondrial defects, stroke-like episodes also occur in aminoacidopathies, urea cycle defects, lysosomal defects, and organic acidemias.<sup>2</sup>

In propionic acidemia, the clinical manifestations of these events can be quite diverse<sup>9,10</sup> (see Table 2 for review of instances of possible metabolic stroke in patients with propionic acidemia, along with respective references). Hemiplegia caused by metabolic stroke in propionic acidemia has been reported a limited number of times in the literature.<sup>11,12</sup> Focal deficits such as hemiparesis/hemiplegia, however, are not always present in metabolic strokes. Encephalopathy is a common initial presentation of metabolic strokes, occurring in 8 of the 10 reported cases (cases 1-3b, 5-7). Seizures were reported in 3 cases (cases 2, 5, and 7). One patient developed choroathetosis, but the period of time of its development after his stroke-like episode is unclear (case 5).<sup>13</sup> Another patient presented with acute extrapyramidal symptoms including Parkinsonian features that responded to treatment with L-DOPA (case 4).<sup>14</sup> Finally, 1 patient died after developing large bilateral hemorrhagic lesions of the basal ganglia (case 6b).<sup>15</sup> In essence, metabolic strokes in propionic acidemia can be associated with a wide spectrum of symptoms, including

**Table 2.** Clinical Findings of Suspected Metabolic Stroke in Patients With PA, Based on Case Reports From the Literature.

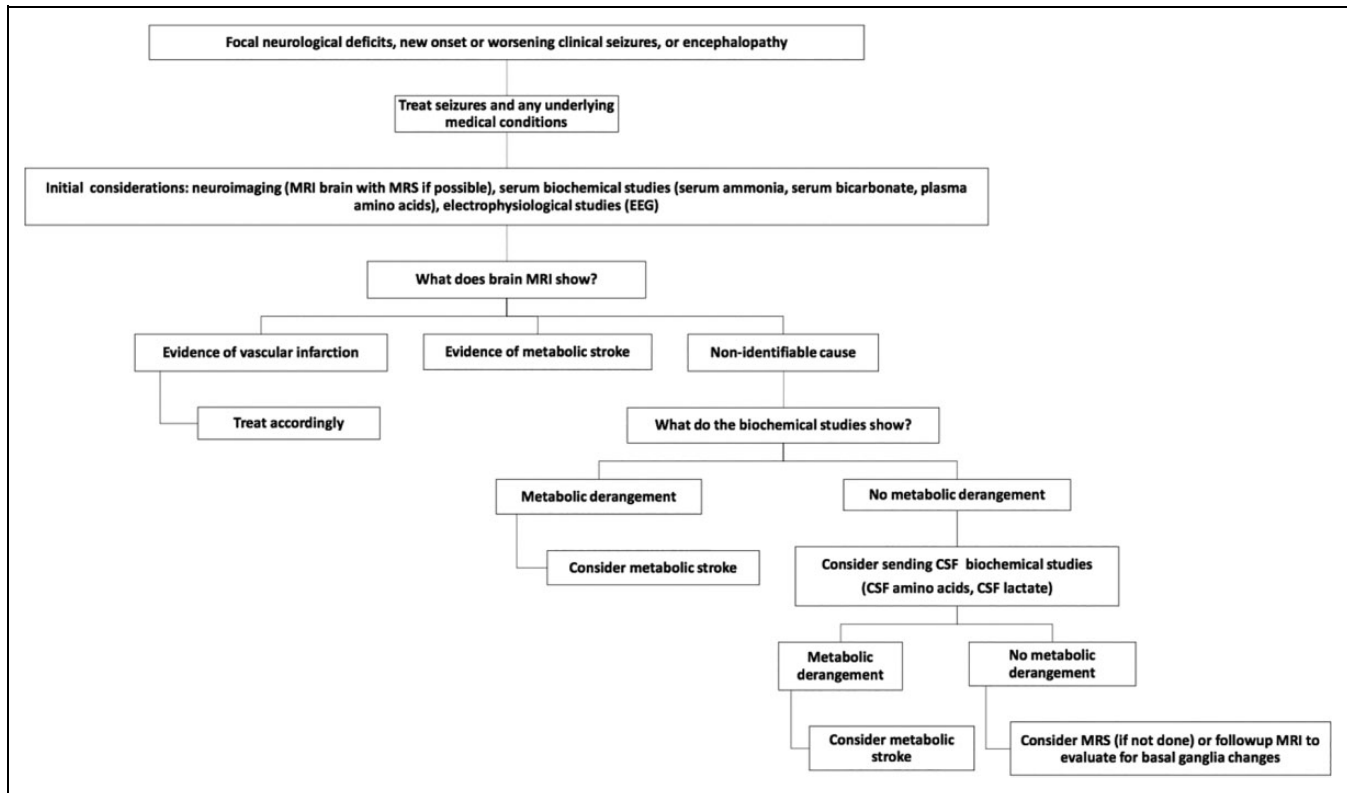
Case Reference	Demographics	Clinical Presentation	Evidence of Significant Metabolic Decompensation		EEG Findings	Brain MRI Findings	Follow-Up
			Plasma	CSF			
1 Karall et al <sup>6</sup>	4-year-2-month-old M	Prolonged GI infection Behavioral changes Regression Confusion Coryza with vomiting Increased drowsiness GTC sz	NR	NR	Generalized diffuse slowing, R > L B/L temporo-occipital sharp waves	Signal abnormality in B/L caudate, putamen, cerebellum	Clinical resolution within a few days
2 Broomfield et al <sup>17</sup>	8-month-old F		Yes	NR	No evidence of ongoing sz activity	Signal abnormality in B/L basal ganglia Signal abnormality in B/L cortical and subcortical regions	Clinical resolution Radiographic resolution within 3 weeks
3a Scholl-Bürgi <sup>11</sup>	9-year-9 month-old F	Drowsiness Vomiting LUE, LLE hemiplegia	No	NR	Generalized diffuse slowing, R > L L central spike waves	Hyperintensity in B/L basal ganglia Hyperintensity in R temporal cortical gray matter	Clinical resolution Radiographic improvement within 3 weeks
3b	10-year-7-month-old F	Drowsiness Bradycardia Hypothermia LUE, LLE hemiplegia	No	NR	Generalized diffuse slowing, R > L B/L temporo-parietal-occipital spike waves	NP	Clinical resolution
3c	10-year-10-month-old F	One week before: hypothermia, paleness, R-sided hemiplegia Paleness Hypothermia	No	Yes	Generalized diffuse slowing, L > R B/L temporo-parietal-occipital regions spike waves, R > L	Hyperintensity in cortical gray matter Hyperintensity in B/L basal ganglia	Clinical resolution within 1 day
4 Burlina et al <sup>4</sup>	15-year-old M	URI symptoms, vomiting 4 days after initial symptoms: dysphagia, sialorrhea, excessive sweating, action tremor 15 days after initial symptoms: Parkinsonian symptoms (amimia, akinesia, hypertonia, cogwheel rigidity, resting tremor)	No	NR	NR	Hyperintensity in B/L caudate and putamen	Radiographic improvement within 6 months Clinical resolution within 1-2 weeks after being treated with L-DOPA
5 Nyhan et al <sup>13</sup>	4-month-old M	Croup Sleepiness Constipation Decreased head control progressing to generalized hypotonia Generalized sz	Yes	NR	Generalized slowing Transient multifocal spikes	Age 13 months: Cerebral atrophy Hyperintensity in B/L basal ganglia	Age 7 years: He required a wheelchair; he was hypotonic, choreoathetotic, dysarthric, with involuntary posturing

(continued)

Table 2. (continued)

Case Reference	Demographics	Clinical Presentation	Evidence of Significant Metabolic Decompensation			Brain MRI Findings	Follow-Up
			Plasma	CSF	EEG Findings		
6a	Haas et al <sup>15</sup> One patient with 2 stroke-like episodes	8-year-old F Lethargy Confusion	NR	NR	NR	Hyperintensity in B/L caudate, putamen, and globus pallidus	Radiographic resolution within 2 months Clinical improvement
6b	9-year-2-month-old F	Disorientation Aphasia Generalized hypotonia	No	No	NR	Infarction of B/L caudate, putamen, and globus pallidus	Death after developing large B/L hemorrhagic lesions of the basal ganglia after second hyperbaric oxygen treatment
7	Shigematsu et al <sup>12</sup> 10-month-old F	Vomiting Drowsiness Fever Generalized sz L-sided hemiplegia	Yes	Yes	NR	Mild brain atrophy, R > L	Clinical improvement within 3 months

Abbreviations: B/L, bilateral; CSF, cerebrospinal fluid; EEG, electroencephalography; F, female; GTC, generalized tonic clonic; L, left; LLE, left lower extremity; LUJ, left upper extremity; M, male; MRI, magnetic resonance imaging; NR, not reported; NP, not performed; PA, propionic acidemia; R, right; sz, seizure.



**Figure 2.** Algorithm for the diagnosis and evaluation of metabolic stroke in propionic acidemia (PA).

hemiparesis, altered mental status, movement disorders, and death.

Typically, stroke-like episodes occur along with evidence of biochemical deterioration (see Table 2).<sup>10</sup> However, in some cases, stroke-related episodes occur without significant metabolic decompensation,<sup>13,14</sup> similar to many of the stroke-like events in our patient. Sometimes, determining metabolic control may require analyzing the cerebrospinal fluid in addition to the plasma. Illustrating this point is the patient described by Scholl-Bürgi et al (the 11-year-old girl with 3 stroke-like episodes during a 13-month period; cases 3a-c). In the first 2 episodes, she exhibited stable metabolic control based on plasma studies. However, during one of the episodes, she had cerebrospinal fluid studies performed in conjunction with plasma studies, and these showed elevated cerebrospinal fluid/plasma ratios for lactate, glutamine, and alanine and normal cerebrospinal fluid/plasma ratios for glycine.<sup>11</sup>

With or without biochemical evidence of metabolic decompensation, the basal ganglia (caudate, putamen, and globus pallidus) remains particularly vulnerable to injury during acute decompensation in propionic acidemia<sup>10</sup> (see Table 2). From these case reports, it is clear that the majority of instances of metabolic stroke are associated with abnormalities in the basal ganglia based on brain MRI. These imaging abnormalities may improve or completely resolve with time. This pattern of basal ganglia injury observed long after previous neurological symptoms have resolved is similar to what was ultimately observed in our patient (in whom the basal ganglia changes on MRI

appeared many years after the first significant event at the age of 3.5 years). At the age of 3.5 years, his brain MRI did not show evidence of basal ganglia involvement. Perhaps injury to the basal ganglia still occurred but was not significant enough to be detected on MRI studies at that time. Presently, MR spectroscopy is of more widespread availability and may be useful to detect biochemical evidence of cerebral dysfunction when routine MRI is unrevealing in cases of suspected metabolic strokes.<sup>1</sup>

In light of the clinical, biochemical, and neuroimaging diversity surrounding these events, we propose MRI along with serum biochemical studies (ammonia, blood gas, and bicarbonate) early on presentation (Figure 2). Electroencephalography may be helpful in cases of encephalopathy or abnormal movements concerning for seizure-like activity. Other triggering events should be explored including blood or cerebrospinal fluid studies to rule out infection, for example. The presence of seizures can greatly confound the clinical picture and exacerbate the patient's status; thus, it is crucial to treat clinical seizures expediently.

Brain MRI can be helpful in differentiating vascular etiologies (such as stroke) from nonvascular etiologies in cases of focal neurological deficits and/or mental status changes. During acute ischemic infarctions, depending on the time of the scan, MRI may show hyperintensity on diffusion-weighted imaging accompanied by hypointensity on apparent diffusion coefficient images. Similarly, during metabolic strokes seen with inborn errors of metabolism and mitochondrial disorders, MRI may also reveal hyperintensity on diffusion-weighted

imaging, but this may be variable or delayed in time, such as exhibited in our patient.

Basic biochemical screening of blood and urine can be used to determine whether the patient is likely in a metabolic state of decompensation (ketoacidosis, hyperammonemia) associated with propionic acidemia. If there is evidence of metabolic derangement accompanying a focal neurological deficit, then the diagnosis of metabolic stroke can be considered.

However, if initial laboratories are normal or equivocal for metabolic decompensation (as in our patient during a few of his presentations), then comparing the cerebrospinal fluid biochemistry profile to the plasma biochemistry profile (amino acids and lactate), or evaluating the cerebrospinal fluid by itself, may draw out evidence of metabolic decompensation. Other forms of secondary biochemical testing to consider at this point are quantitative urine organic acids and plasma acylcarnitine profile. If these additional cerebrospinal fluid/urine/blood tests still do not suggest metabolic decompensation, then a metabolic stroke may be less likely. Magnetic resonance spectroscopy may be helpful in evaluating metabolite alterations associated with acute decompensation.<sup>18</sup> Recent guidelines emphasized the importance of MRI especially during episodes of acute neurological changes.<sup>7</sup>

As evidenced by our patient, the spectrum of presentations for metabolic stroke can be diverse, and during any individual episode, it may be difficult to obtain all of the studies needed to fully convince oneself that this is the appropriate diagnosis. If the etiology of any given episode is unclear, over time, the pattern of neuroimaging should help clarify the issue. Importantly, the potential for reversibility of quite dramatic physical examination findings such as marked hemiparesis should be kept in mind. This should help improve prognostic counseling of patients with propionic acidemia and related organic acidemias.

### Acknowledgments

The authors would like to thank the patient and his family.

### Author contributions

SS, MA, and JMC contributed to conception and design, drafted the manuscript, critically revised the manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. SS and MA contributed to analysis and interpretation. JMC contributed to acquisition, analysis, and interpretation.

### Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.


### Ethical Approval

All the data described in this case report are aligned with Johns Hopkins University ethics. No required written IRB consent for case report in our institution.

### Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

### ORCID iD

Siddharth Srivastava  <https://orcid.org/0000-0001-7008-1879>

### References

1. Pavlakis SG, Kingsley PB, Bialer MG. Stroke in children: genetic and metabolic issues. *J Child Neurol.* 2000;15(5):308-315.
2. Hoffmann GF, Zschocke J, Nyhan WL. *Inherited Metabolic Diseases: A Clinical Approach.* Berlin, Germany: Springer; 2010.
3. Fenton W, Gravel R, Rosenblatt D. Disorders of propionate and methylmalonate metabolism. In: Scriver C, Beaudet A, Sly W, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Diseases.* New York, NY: McGraw-Hill; 2001:2165-2193.
4. Wolf B, Hsia YE, Sweetman L, Gravel R, Harris DJ, Nyhan WL. Propionic acidemia: a clinical update. *J Pediatr.* 1981;99(6):835-846.
5. Schreiber J, Chapman KA, Summar ML, et al. Neurologic considerations in propionic acidemia. *Mol Genet Metab.* 2012;105(1):10-15. doi:10.1016/j.ymgme.2011.10.003.
6. North KN, Korson MS, Gopal YR, et al. Neonatal-onset propionic acidemia: neurologic and developmental profiles, and implications for management. *J Pediatr.* 1995;126(6):916-922.
7. Baumgartner MR, Hörster F, Dionisi-Vici C, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. *Orphanet J Rare Dis.* 2014;9:130. doi:10.1186/s13023-014-0130-8.
8. Grünert SC, Müllerleile S, De Silva L, et al. Propionic acidemia: clinical course and outcome in 55 pediatric and adolescent patients. *Orphanet J Rare Dis.* 2013;8:6. doi:10.1186/1750-1172-8-6.
9. Gascon GG, Ozand PT, Brismar J. Movement disorders in childhood organic acidurias. Clinical, neuroimaging, and biochemical correlations. *Brain Dev.* 1994;16(suppl):94-103.
10. Sutton VR, Chapman KA, Gropman AL, et al. Chronic management and health supervision of individuals with propionic acidemia. *Mol Genet Metab.* 2012;105(1):26-33. doi:10.1016/j.ymgme.2011.08.034.
11. Scholl-Bürgi S, Haberlandt E, Gotwald T, et al. Stroke-like episodes in propionic acidemia caused by central focal metabolic decompensation. *Neuropediatrics.* 2009;40(2):76-81. doi:10.1055/s-0029-1231065.
12. Shigematsu Y, Mori I, Nakai A, et al. Acute infantile hemiplegia in a patient with propionic acidemia. *Eur J Pediatr.* 1990;149(9):659-660.
13. Nyhan WL, Bay C, Beyer EW, Mazi M. Neurologic nonmetabolic presentation of propionic acidemia. *Arch Neurol.* 1999;56(9):1143-1147.
14. Burlina AP, Baracchini C, Carollo C, Burlina AB. Propionic acidemia with basal ganglia stroke: treatment of acute extrapyramidal symptoms with L-DOPA. *J Inher Metab Dis.* 2001;24(5):596-598.
15. Haas RH, Marsden DL, Capistrano-Estrada S, et al. Acute basal ganglia infarction in propionic acidemia. *J Child Neurol.* 1995;10(1):18-22.
16. Karall D, Haberlandt E, Schimmel M, et al. Cytotoxic not vasogenic edema is the cause for stroke-like episodes in propionic acidemia. *Neuropediatrics.* 2011;42(5):210. doi:10.1055/s-0031-1287772.



17. Broomfield A, Gunny R, Prabhakar P, Grunewald S. Spontaneous rapid resolution of acute basal ganglia changes in an untreated infant with propionic acidemia: a clue to pathogenesis? *Neuropediatrics*. 2010;41(6):256-260. doi:10.1055/s-0031-1273720.
18. Davison JE, Davies NP, Wilson M, et al. MR spectroscopy-based brain metabolite profiling in propionic acidemia: metabolic changes in the basal ganglia during acute decompensation and effect of liver transplantation. *Orphanet J Rare Dis*. 2011;6:19. doi:10.1186/1750-1172-6-19.