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Case report

Unique neuroradiological findings in propionic acidemia

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ABSTRACT

Propionic acidemia is a rare metabolic disorder that affects the catabolism of branched-chain amino acids and oddchain fatty acids. Propionic acidemia is one of the least common organic acidemias. Presented here are manifestations not previously characterized. The first case is an infant with diffuse subcortical diffusion restriction and vermian atrophy. The second case is an adolescent with asymmetric cortical volume loss and contralateral cortical diffusion restriction. These unique brain MRI findings of propionic acidemia may aid the neuroradiologist in guiding genetic testing for occult metabolic disease.

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Introduction

The organic acidemias are a group of metabolic disorders in which a build-up of organic acids in the blood takes place due to an enzyme deficiency. Since the build-up of metabolites is excreted in the urine, organic acidemias are also referred to as organic acidurias.

The amino acids valine, isoleucine, threonine, and methionine as well as odd chain fatty acids and cholesterol side chains are catabolized into the 3-carbon substrate propionyl-CoA, which under normal physiologic conditions is con-

verted to the 4-carbon metabolite methomalonyl-CoA in the presence of the biotin-dependent mitochondrial enzyme propionyl-CoA carboxylase. The enzyme is a dodecamer of 6 alpha and 6 beta subunits, and mutation to either of the encoding genes PCCA (on chromosome 13q32.3) or PCCB (on chromosome 3q22.3) inherited in a homozygous recessive fashion can result in the accumulation of propionyl-CoA and eventually propionic acid resulting in the disorder propionic acidemia [1]. Propionic acidemia is one of the rarer organic acidemias and occurs in approximately 1 in 100,000 to 1 in 150,000 people [2].

The disease typically presents in the neonatal period. Less common forms presenting later in life, however, have

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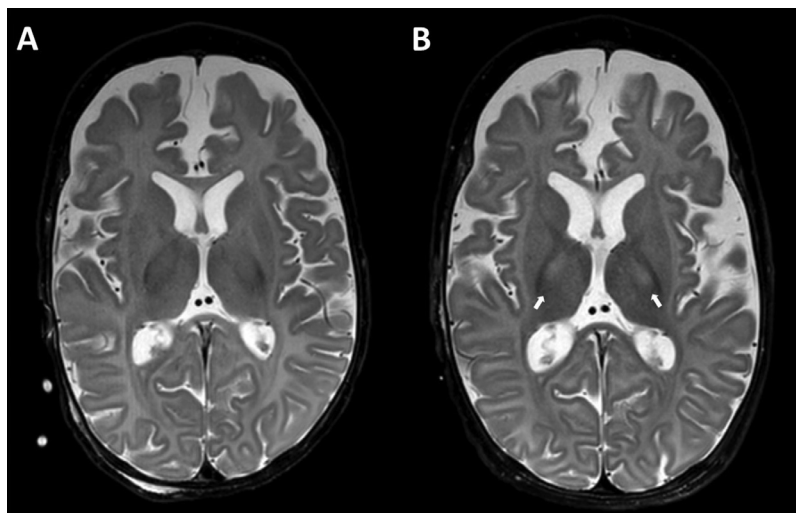


Fig. 1 – Axial T2-weighted images of the brain were acquired at 3.0 T on a Philips Ingenia MRI system. Shown here are images of a 3-month-old male at baseline (A) and during an acute propionic acidemia crisis at 5 months of age (B). White arrows in (B) indicate T2 hyperintense signal in the ventral thalami.

been described. Clinical features of the organic acidemias in the newborn include poor feeding, hypotonia, vomiting, and lethargy. Patients are also prone to seizures, and propionic acidemia may manifest as failure to thrive in older children. If a metabolic crisis is left unrecognized or untreated, coma, and death can ensue.

The rarity of the disease has resulted in few published cases, but case series have been described. Common findings reported include T2/fluid-attenuated inversion recovery hyperintensity in the putamina and caudate nuclei, generalized brain swelling, and delayed myelination [3–5].

We present unique neuroradiological findings in an infant and an adolescent with different and unique manifestations of propionic acidemia exacerbation.

Case report 1: infant

The first patient was a 5-month-old male transferred to our tertiary care center with increased vomiting and lethargy. The patient had been followed by the genetics service and was known to carry an in-frame deletion of a single amino acid in the PCCA gene. He had been admitted several times previously for propionic acidemia crises, and a prior magnetic resonance imaging (MRI) obtained at 3 months of age was available (Figs. 1A, 2A, and 3A). Comorbidities included hyperparathyroidism, hypocalcemia, and *Clostridium difficile* diarrhea. His laboratory studies included a white blood cell count of 2.2 cells/mm³, ammonia of 127 μmol/L, lactate of 2.7 mmol/L, ionized calcium of 1.19 mg/dL, and glucose of 242 mg/dL. The basic metabolic panel revealed a sodium of 132 mEq/L, a potassium of 5.1 mEq/L, bicarbonate of 13 mEq/L, blood urea nitrogen of 48 mg/dL, creatinine of 0.6 mg/dL, and a chloride of 99 mEq/L.

The child became increasingly lethargic on hospital day 4 and underwent an MRI which revealed increased T2 signal in the ventral thalami and parenchymal volume loss in compari-

son to the examination obtained 2 months prior with resulting prominence of the lateral ventricles and cortical sulci (Fig. 1B). There was also marked volume loss in the vermis (Fig. 2B). The most striking feature was a diffuse symmetric subcortical pattern of diffusion restriction (Fig. 3B), in addition to diffusion restriction of the basal ganglia and thalami. No seizures were observed. An electroencephalogram performed on hospital day 4 showed slowing consistent with metabolic encephalopathy. The patient was eventually discharged from the hospital after a 24-day course without additional encephalopathic changes or neurologic imaging.

Case report 2: adolescent

This child was a 15-year-old female who presented to the emergency department with a headache and increased sleepiness. She had been followed by the genetics service since birth with propionic acidemia, which had been confirmed by genetic testing during infancy. Her younger sister also had confirmed propionic acidemia. The patient's past medical history was significant for developmental delay and seizure-like activity with electroencephalography suggesting abnormal activity throughout the right hemisphere. MRI had been performed 10 months previously at age 14 during a metabolic crisis (Figs. 4A and 5A) and was repeated shortly after this admission (Figs. 4B and 5B). At admission, her ammonia level was 63 μmol/L.

Asymmetric volume loss was apparent throughout the right hemisphere with subsequent asymmetric prominence of the cortical sulci and extra axial spaces, a finding that was relatively unchanged in comparison to the previous MRI (Fig. 4). New volume loss was now apparent throughout the left cerebral hemisphere (Fig. 4B). Asymmetric cortical diffusion restriction involving the left hemisphere and right occipital lobe apparent during a metabolic crisis (Fig. 5A) had resolved (Fig. 5B).

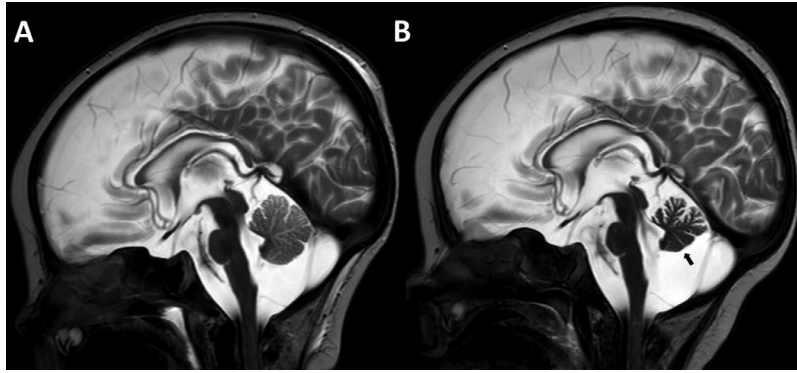


Fig. 2 – Sagittal T2-weighted images of the brain were acquired at 3.0 T on a Philips Ingenia MRI system. Shown here are images of a 3-month-old male at baseline (A) and during an acute propionic acidemia crisis at 5 months of age (B). The black arrow in (B) indicates marked vermian atrophy.

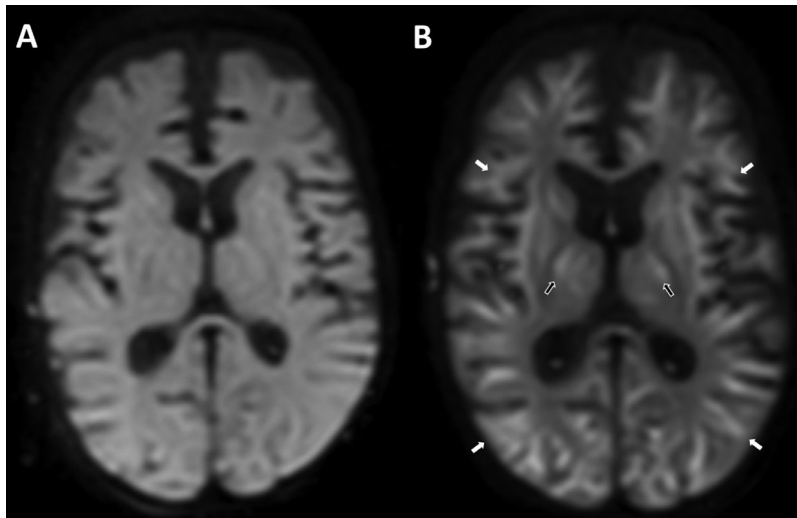


Fig. 3 – Axial diffusion-weighted images of the brain were acquired at 3.0 T on a Philips Ingenia MRI system. Shown here are images in a 3-month-old male at baseline (A) and during an acute propionic acidemia crisis at 5 months of age (B). Diffusion bright signal is seen diffusely throughout the subcortical white matter (white arrows) as well as the ventral thalami (black arrows) and basal ganglia. Diffusion restriction was confirmed on ADC (not shown).

Discussion

Published neuroradiologic manifestations of propionic acidemia are less common than methylmalonic acidemia [3], though both disorders are usually described in tandem. The most typical imaging finding in propionic acidemia has been cited as bilateral basal ganglia disease [6]. Several striking findings witnessed here have not previously suggested as characteristic associations with propionic acidemia.

The cases depicted here show unique patterns of diffusion restriction in this disorder. In the first case, the diffuse subcortical pattern of diffusion restriction is an interesting unique manifestation of propionic acidemia. In the second case, diffusion restriction was cortically based and spared areas of brain atrophy. This could suggest that previously affected cortex may be refractory to subsequent attacks.

Subsequent atrophy of the affected structures is typical for organic acidemia crises; however, this case highlights significant vermian volume loss in the case of the first patient with propionic acidemia. The vermis has been previously reported to be relatively unaffected in propionic acidemia [7], which makes this case a departure from prior literature. The asymmetric atrophy in the second patient suggests that some element of volume loss may be long-lasting or permanent even in the absence of visible cystic encephalomalacia.

Both cases here show diffusion restriction in patterns not consistent with major vascular distributions. This has important clinical implications, as the findings seen here both provide a source of encephalopathy observed by the ordering provider and suggest a nonvascular etiology for the patient's presentation. The patterns of disease observed in these patients may serve to prompt genetic testing and steer clin-

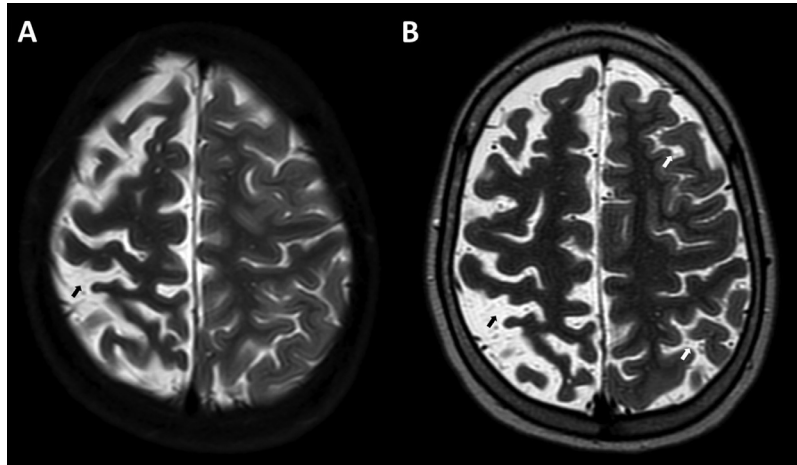


Fig. 4 – Axial T2-weighted images of the brain were acquired at 3.0 T on a Philips Ingenia MRI system (A) and at 1.5 T on a Philips Achieva MRI system (B). Shown here are images of a 14-year-old female during an acute propionic acidemia crisis (A) and 10 months later without crisis (B). Prominence of the extra-axial CSF in the setting of cortical volume loss throughout the superior right hemisphere was relatively unchanged (black arrows). Left-sided atrophy (white arrows) was more pronounced following the crisis. Note: An mDIXON fat suppression technique was applied in (A) but not in (B) which accounts for the differential appearance of the skull and extracranial structures.

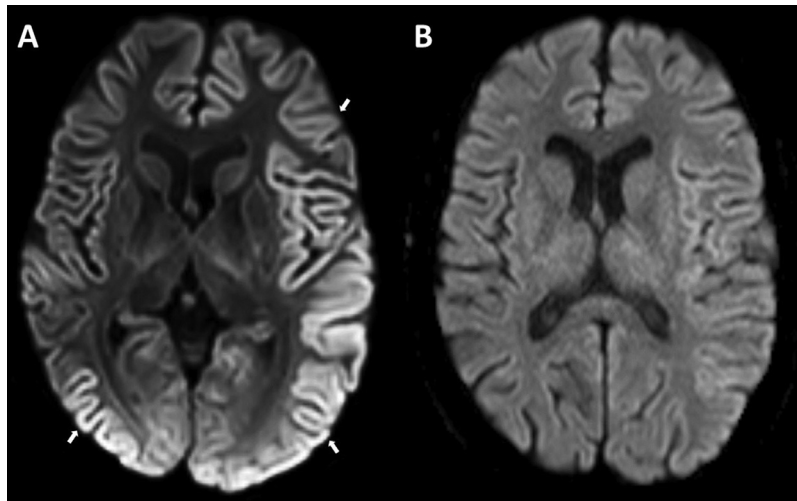


Fig. 5 – Axial diffusion-weighted images of the brain were acquired at 3.0 T on a Philips Ingenia MRI system (A) and a 1.5 T Philips Achieva MRI system (B). Shown here are images of a 14-year-old female during an acute propionic acidemia crisis (A) and 10 months later without crisis (B). Diffusion bright signal is present throughout the cortex of the left hemisphere and right occipital lobe (white arrows). Diffusion restriction was confirmed on ADC (not shown). The right temporal and frontal lobes are spared.

ical management, which includes dietary therapy. The lack of previously seen diffusion restriction in the second patient was helpful for the clinical team in that it suggested that her clinical presentation was not due to an acute exacerbation of her disease, and she was discharged shortly after the MRI.

Several caveats are noteworthy. In the first case, the patient was not imaged after recovering from the exacerbation. As such, it remains unknown whether the atrophic changes throughout the brain are reversible for this infant or if they persist between attacks. The diffusion restriction and sub-

sequent atrophy could potentially be explained by hypoxemia in the setting of pancytopenia. The diffuse subcortical pattern, however, would be less typical for central asphyxia which more commonly manifests as pronounced changes in the central grey nuclei. Additionally, this patient returned to functional baseline prior to discharge as had been the case with prior exacerbations. It has been shown that diffusion restriction, during propionic acidemia crisis is reversible, when the metabolic imbalance is corrected [8]. The possibility of medication-related cerebellar volume loss should also be considered.

In the second case, the cortical pattern of diffusion restriction observed during exacerbation could be explained by subclinical seizures. Her primary clinical harbinger of metabolic crisis was lethargy rather than seizure activity, and her seizures had been reportedly controlled on anti-epileptic medication. The fact that the cortical diffusion restriction spared the most atrophic portions of the brain is notable nonetheless. Volume loss in epilepsy-associated metabolic syndromes could be the result of chronic seizures in general.

Conclusion

Diffuse subcortical diffusion restriction, vermian atrophy, and unilateral-predominant cortical diffusion restriction can be seen in the setting of acute metabolic crises observed in propionic acidemia. The neuroradiologist may be the first to suggest genetic testing based on these unique findings.

REFERENCES

- [1] Maoli I, Venditti CP. Disorders of branched chain amino acid metabolism. *Transl Sci Rare Dis* 2016;7:91–110.
- [2] Baumgartner MR, Hörster F, Dionisi-Vici C, Haliloglu G, Karall D, Chapman KA, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. *Orphanet J Rare Dis* 2014;9:130.
- [3] Brismar J, Ozand PT. CT and MR of the brain in disorders of the propionate and methylmalonate metabolism. *AJNR Am J Neuroradiol* 1994;15:1459–73.
- [4] Bergman AJ, Van der Knaap MS, Smeitnik JA, M Duran M, Dorland L, Valk J, et al. Magnetic resonance imaging and spectroscopy of the brain in propionic acidemia: clinical and biochemical considerations. *Pediatr Res* 1996;40:404–9.
- [5] Al-Essa M, Bakheet S, Patay Z, Al-Shamsan L, Al-Sonbul A, Al-Watban J, et al. 18Fluoro-2-deoxyglucose (18FDG) PET scan of the brain in propionic acidemia: clinical and MRI correlations. *Brain Dev* 1999;21:312–17.
- [6] Patay Z. Metabolic disorders. In: Tortori-Donati P, editor. *Pediatric Neuroradiology*. Berlin, Germany: Springer-Verlag; 2005. p. 587.
- [7] Patay Z. Metabolic disorders. In: Tortori-Donati P, editor. *Pediatric Neuroradiology*. Berlin, Germany: Springer-Verlag; 2005. p. 588.
- [8] Kandel A, Amatya SK, Yeh EA. Reversible diffusion weighted imaging changes in propionic acidemia. *J Child Neurol* 2013;28:128–31.