Clinical Reasoning: A young man with progressive subcortical lesions and optic nerve atrophy

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SECTION 1

The male patient is the third child of unrelated Japanese parents. His older sister had tachypnea and feeding difficulties, and died at 5 days of age. The patient was delivered at term (birthweight, 3.8 kg), following an unremarkable pregnancy. He

presented with tachypnea, metabolic acidosis, and hyperammonemia ($944 \mu\text{mol} \cdot \text{L}^{-1}$) at 6 days.

Questions for consideration:

1. What is the differential for infantile presentation of hyperammonemia in the neonatal period?
2. What laboratory tests would you pursue?

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SECTION 2

Hyperammonemia occurs in urea cycle disorders (e.g., ornithine transcarbamylase deficiency) and organic acidurias (e.g., methylmalonic aciduria, propionic aciduria, and isovaleric aciduria) and fatty acid oxidation defects (e.g., multiple acyl-CoA dehydrogenase deficiency). The existence of acidosis with ketosis indicates organic aciduria, whereas respiratory alkalosis is observed in urea cycle defects. Diagnosis is based on quantitative assay of amino acids and acylcarnitines from dried blood and organic acids in urine samples.

Case: part 2. Elevated levels of 2-methylcitric acid and 3-hydroxypropionic acid were found in the urine. The plasma propionic acid concentration was increased ($4.5 \text{ mg} \cdot \text{dL}^{-1}$), and propionyl-CoA carboxylase (PCC) activity in fibroblasts was decreased ($6.3 \text{ pmol} \cdot \text{min}^{-1} \cdot \text{mg}^{-1}$ protein, normal value: $292 [n = 4]$). The patient was treated with exchange transfusion, peritoneal dialysis, high-calorie infusions, and a low-protein diet.

Questions for consideration:

1. What is the diagnosis?
2. How should these infants be treated in the acute period?
3. What treatment should be given long term?

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SECTION 3

Propionic aciduria is an autosomal recessive disease caused by a deficiency of PCC. PCC is a biotin-dependent enzyme that catalyzes the branched chain amino acids valine and isoleucine but not leucine; it also catalyzes methionine, threonine, and odd-chain fatty acids in the mitochondrial matrix. PCC is composed of α and β subunits, which are encoded by nuclear genes *PCCA* and *PCCB*, respectively. PCC deficiency causes accumulation of propionic acid, 3-hydroxypropionic acid, 2-methylcitric acid, and propionylglycine in blood, urine, and CSF.¹

Clinical forms of propionic aciduria are described on the basis of the age at onset: neonatal and late onset. The neonatal-onset form is characterized by poor sucking, vomiting, failure to thrive, and progressive encephalopathy. Routine laboratory findings are metabolic acidosis, ketosis, lactic acidosis, hyperammonemia, leukocytopenia, thrombocytopenia, and anemia. The late-onset form is characterized by periodic vomiting to life-threatening hyperammonemia, psychomotor retardation, and other chronic symptoms.¹ Propionic aciduria is characterized by increased excretion of propionic acid, 3-hydroxy propionic acid, and 2-methylcitric acid in urine as well as elevated concentrations of propionyl-carnitine in blood serum or plasma. It is initially diagnosed based on enzymatic analysis of propionyl-CoA carboxylase activity in fibroblasts or leukocytes. Identification of the specific mutations in *PCCA* or *PCCB* is required to confirm the diagnosis.¹

The increased 2-methylcitric acid and 3-hydroxypropionic acid levels and decreased propionyl-CoA carboxylase activity in this case indicated propionic aciduria. Mutation analysis revealed homozygosity for p.Thr428Ile in the *PCCB* gene, confirming propionic aciduria.

Emergency treatment for propionic aciduria involves low-protein, high-energy nutrition and rehydration. Almost all propionic aciduria patients show hyperammonemia, which results from inhibition of

urea cycle enzymes by accumulated acyl-CoA esters. Some patients, especially those severely affected, require hemodialysis/hemofiltration. Sodium benzoate and carbamyl glutamate are used to treat secondary hyperammonemia.² Long-term management comprises low-protein diet and carnitine supplementation. Arginine and carnitine are administered for detoxification of toxic metabolites. Metronidazole is often administered to reduce production of propionic acid by gut bacteria.¹

Case: part 3. After emergency intervention, the patient was treated with a low-protein diet and carnitine supplementation. During the first 5 years of life, he had several episodes of metabolic acidosis requiring hospitalization; however, he never showed metabolic decompensation thereafter. Despite nearly normal development at 4 years, he thereafter developed intellectual deficits that gradually deteriorated with age: his developmental quotient was 88 at the age of 4 and 74 at 6, while his IQ was 73 at the age of 7 and 54 at 15.

At 22 years, metronidazole administration was initiated to reduce propionic acid production by gut bacteria. Bilateral vision impairment was also detected during a regular health check-up. Ophthalmologic examination showed temporal pallor of the right eye and left optic nerve atrophy (figure 1). The patient's visual acuity was 20/200 in the right eye and 20/300 in the left eye. In both eyes, his visual fields showed central scotoma, and his visual evoked potential (VEP) displayed decreased amplitude. An electroretinogram showed normal findings, while optical coherence tomography revealed no retinal structure abnormalities. Within a year, his visual acuity decreased from 20/200 to hand motion in the right eye and from 20/300 to counting fingers in the left. He also had intention tremor, mild hyperammonemia, and elevated lactic acid levels, but no metabolic acidosis. Ophthalmologic examination results at 11 years were normal.

Brain MRI revealed symmetric lesions of the basal ganglia, including the caudate nucleus, putamen, and globus pallidus (figure 2A). At 23 years, no symptoms were present, but diffusion-weighted MRI of the brain showed subcortical lesions (figure 2, B–D). At 24 years, he showed acute reversible muscle weakness and dysarthria, comparable to pseudobulbar paralysis. Neurologic evaluation showed increased deep tendon reflexes on the left side of the body, while subsequent MRI of the brain revealed progression of the subcortical lesions (figure 2, E–G), without evidence of metabolic decompensation.

Figure 1 Fundal images

Temporal pallor in the right eye and optic nerve atrophy in the left.

(A, B, E) T2-weighted images; the arrows in A indicate the high intensity of basal ganglia areas. (C, F) Fluid-attenuated inversion recovery. (D, G) Diffusion-weighted imaging, showing abnormal signals in subcortical lesions.

At 24 years, chest radiography showed an increased cardiothoracic ratio (65%) and pulmonary edema. Echocardiogram showed dilated hypokinetic left ventricle and a decrease in ejection fraction (48%), resembling dilated cardiomyopathy. The patient was administered furosemide, spironolactone, and carvedilol.

Questions for consideration:

1. Why did this patient's condition deteriorate even without metabolic acidosis crises?
2. What is the range of prognosis for neonatal-onset form propionic aciduria?
3. What type of monitoring will he need?

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SECTION 4

The accumulation of toxic organic acids causes cerebral stroke that cannot be accounted for by hypoxemia or vascular insufficiency: this neurologic event is termed metabolic stroke.³ Toxic metabolites cause secondary mitochondrial dysfunction, which leads to metabolic stroke.⁴ According to the recent “trapping hypothesis,” the limited transport of toxic metabolites from the brain to the blood compartment leads to accumulation of toxic dicarboxylic acids in glutaric aciduria type I and methylmalonic aciduria.⁵ Like propionic aciduria, methylmalonic aciduria is also a branched-chain amino acid disorder. For propionic aciduria patients, accumulation of the dicarboxylic acid 2-methylcitric acid seems likely; however, it has not yet been sufficiently documented.

Patients with propionic aciduria and methylmalonic aciduria often present with mental retardation, epilepsy, and extrapyramidal symptoms. Sixty percent of patients with propionic aciduria have an IQ lower than 75.² Symmetric lesions of the basal ganglia are the most frequently reported MRI changes in propionic aciduria and methylmalonic aciduria.² Subcortical white matter abnormality was additionally reported in 11.5% of patients with methylmalonic aciduria.⁶ However, these findings have not been confirmed in propionic aciduria, probably because the number of patients is relatively small.

Compared to previously reported late-onset optic nerve atrophy in patients with methylmalonic aciduria and propionic aciduria,⁷ our patient is the oldest. The previous report suggested that optic nerve atrophy observed in propionic aciduria and methylmalonic aciduria resembled Leber hereditary optic neuropathy (LHON),⁷ as both showed optic nerve atrophy and normal retina. LHON is caused by 1 of 3 pathogenic mtDNA mutations at the nucleotide positions 11,778, 3,460, and 14,484, located in genes encoding the mitochondrial complex I subunits. Our patient carried none of these mutations. The common findings between optic nerve atrophy in propionic aciduria/methylmalonic aciduria and LHON suggest that secondary mitochondrial dysfunction leads to optic nerve atrophy in patients with propionic aciduria and methylmalonic aciduria. Optic nerve atrophy is age-dependent, but independent of metabolic control, other neurologic complications, and overall health status.⁷ Therefore, we recommend regular ophthalmologic examination of patients with propionic aciduria and methylmalonic aciduria.

In many countries, propionic aciduria is targeted in newborn screening programs. About 60% of patients diagnosed through newborn screening were already symptomatic and less than 10% remained

asymptomatic.⁸ Even though newborn screening diagnosis does not positively correlate with a milder clinical course or better neurologic outcome,⁸ it is important from the viewpoint of earlier diagnosis and decreased early mortality.

According to genotype and phenotype correlation analysis, certain null mutations are related to neonatal onset, while certain missense mutations are related to the late-onset form.⁹ Although late-onset patients have higher survival rates compared to neonatal-onset patients,⁹ both face the risk of relapses of life-threatening episodes of metabolic decompensation and risk of death or further neurologic damage.

PCC plays a role mainly in the liver; therefore, liver transplantation has been considered an alternative therapy.² Liver transplantation minimizes further metabolic acidosis and improves the quality of life. However, various complications, including basal ganglia lesions, cardiomyopathy, and optic nerve atrophy, were reported in patients without metabolic decompensation.^{2,7} Even after liver transplantation, stroke-like episodes or cardiomyopathy was reported.¹⁰

Thus, conventional management is insufficient to improve the long-term prognosis for propionic aciduria patients, indicating the need for novel therapeutic approaches based on a better understanding of the pathophysiology.

AUTHOR CONTRIBUTIONS

Shoko Komatsuzaki contributed to conceptualizing the study and design, analysis and interpretation of data, drafting/revising the manuscript. Osamu Sakamoto contributed to the analysis and interpretation of the data, drafting/revising the manuscript. Nobuo Fuse contributed to the analysis and interpretation of data, drafting/revising the manuscript. Mitsugu Uematsu contributed to the analysis and interpretation of data, drafting/revising the manuscript. Yoichi Matsubara contributed to drafting/revising the manuscript. Toshihiro Ohura contributed in critical review of the manuscript, reviewed the literature for manuscript preparation, and supervised the clinical management of study patients.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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