Neurologic Nonmetabolic Presentation of Propionic Acidemia

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Background: Patients with propionic acidemia usually present in the neonatal period with life-threatening ketoacidosis, often complicated by hyperammonemia. It was thought that the neurologic abnormalities seen in this disease were exclusively the consequences of these acute crises. Experience with 2 patients with propionic acidemia indicates that this disease may present first with prominent neurologic disease without the life-threatening episodes of ketoacidosis that usually serve as the alerting signals for a diagnosis of an organic acidemia.

Objective: To examine the clinical and metabolic aspects of 2 patients with a phenotype that suggested disease of the basal ganglia.

Design: Examination of patterns of organic acids of the urine and enzyme assay for propionyl-CoA carboxylase in fibroblasts and lymphocytes.

Setting: Referral population to a biochemical genetics laboratory.

Patients: Two patients whose prominent features were hypotonia followed by spastic quadriparesis and choreoathetosis. Both had seizures. One patient was mildly mentally retarded but grew normally physically. The other had profound mental retardation and failure to thrive; he also self-mutilated his lower lip. Self-injurious behavior has not been reported in this disease.

Main Outcome Measures: Clinical description, blood ammonia levels, organic acid levels in the urine, and enzyme activity.

Results: Excretion of metabolites, including methylcitrate, was typical. Residual activity of propionyl-CoA carboxylase approximated 5% of the control in each patient.

Conclusions: Propionic acidemia can present as a pure neurologic disease without acute episodes of massive ketoacidosis. Hyperammonemia may occur after infancy in some patients, presenting as Reye syndrome.

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Propionic acidemia is an inborn error of amino acid catabolism in which the fundamental expression of the abnormal gene is the virtually complete absence of activity of propionyl-CoA carboxylase. The usual clinical presentation involves potentially lethal episodes of ketosis and metabolic acidosis. Mortality in infancy is high.

It has long been recognized that this disorder can produce neurologic abnormalities. However, the disorder virtually always presents in the early days of life with vomiting, ketosis, and acidosis progressive to coma; it often results in death. In those recovering from the acute episode there may be damage to the nervous system as a result of diminished perfusion of the brain. Furthermore, the early infantile episodes of metabolic imbalance are often complicated by hyperammonemia that may damage the brain. It was thought that the cerebral and neurologic sequelae of this disease result exclusively from these early insults to the central nervous system, and a number of teenagers and young adults have been observed whose central nervous system function is normal. It has recently been recognized that metabolic stroke and particularly infarction of the basal ganglia may be a complication of this disease, as it is of methylmalonic acidemia. However, the patients with this complication have presented with the usual neonatal ketoacidosis; most have had many ketoacidotic episodes, and usually the stroke has complicated such an episode.

It is the purpose of this study to show that propionic acidemia can have a purely neurologic presentation in which the patient develops advanced central nervous system disease without the expected heralding ketoacidotic attacks.
Organic acid analysis was performed as described by Hoffmann et al. The activity of carboxylases in lymphocytes and cultured fibroblasts was measured as described by Weyler et al.

### REPORT OF CASES

#### CASE 1

A 20-year-old man of Amish descent presented with recurrent fever, spastic quadriplegia, choreoathetosis, and self-mutilation of the lower lip. His mother was a 29-year-old gravida 3 para 3 white woman, who was the second cousin of his father. The prenatal and perinatal histories were unremarkable except for a nuchal cord. The patient appeared healthy until age 3 months, when his mother noticed he could no longer hold his head up. He was cared for in a nursing home from age 4 months. There was a history of renal calculi. At age 15 years, he was admitted to the hospital for fever and dehydration. During 2 months in the hospital his temperature ranged from 38.4°C to 41.1°C. He experienced seizures, several urinary tract infections, pneumothoraces, and gastrointestinal bleeding, one instance of which necessitated a transfusion. He had several episodes of hyperammonemia. Analysis of liver biopsy specimens led to a diagnosis of Reye syndrome. Reevaluation of the slides confirmed the presence of microvesicular fat. Platelet counts on this admission were as low as 29 × 10⁹/L. Hemoglobin levels were as low as 72 g/L. Examination of the bone marrow revealed a hypocellular marrow. The concentration of ammonia was as high as 277 µmol/L (388 µg/dL), and 8 values higher than 150 µmol/L (210 µg/dL) were obtained. Aspartate aminotransferase levels were as high as 209 U/L; alanine aminotransferase, 99 U/L. The bicarbonate values ranged from 21 to 27 mmol/L. Initial concentrations of glucose were 1.1 and 1.8 mmol/L (20 and 32 mg/dL).

The findings from physical examination on admission revealed a weight of 24.1 kg, which is at the 50th percentile for a child aged 6 years. Head circumference was 50.3 cm (50th percentile for a 3-year-old child). He seemed spastic, athetoid, and cachectic. He was markedly hypertonic, but all of the joints except the knees could be fully extended passively. Plantar responses were flexor. There was mild plagiocephaly and overfolding of the superior helix of each ear. The lower lip had loss of tissue in 2 lateral clefts with bulbous tissue in the center. Developmental testing demonstrated gross and fine motor skills at the 0- to 4-week age level. He had a vocabulary of a few words, but they were extremely difficult to understand.

Laboratory evaluation revealed a hemoglobin level of 79 g/L, a platelet count of 155 × 10⁹/L, and concentration of bicarbonate of 23 mmol/L. The ammonia value was 98 µmol/L (137 µg/dL). Analysis of the amino acids of the plasma revealed a normal concentration of glycine, 97 µmol/L. The urinary glycine content of 13 mmol per mole of creatinine was also normal. Results of assay of hypoxanthine phosphoribosyltransferase and very-long-chain fatty acids were normal. A diagnosis of probable propionic acidemia was made on the basis of quantification of the organic acids of the urine before and after dietary treatment (Table), and the presence of propionyl carnitine in the acylcarnitine profile of the blood was consistent with this diagnosis. Results of assay of cultured fibroblasts revealed deficient activity of propionyl-CoA carboxylase. Lymphocyte activity was 11 pmol/min per milligram of protein, which was 5% of a simultaneous control. Complementation analysis indicated that the patient was in the BC complementation group.

A magnetic resonance image of the brain showed moderate generalized cerebral cortical atrophy and bilateral symmetric atrophy of both caudate nuclei. Echo-cardiographic findings revealed a dilated aortic root and trivial aortic valvular insufficiency. The patient died of airway obstruction during sleep at age 22 years.

#### CASE 2

An 8-year-old boy was first diagnosed as having propionic acidemia at age 7 months. He was the first born and delivered at term of a healthy mother (nonconsanguineous parents) by cesarean section following breech presentation. Birth weight was 4247 g. He seemed healthy until age 4 months and had developed the ability to grasp objects and hold his head at 90° when prone. He was breast-fed and had begun to eat rice cereal, fruits, and vegetables.

At age 4 months, he had had croup for a few days, treated at home. A few days later he slept longer than usual and developed constipation and decreased head control.
Within 2 hours, he had become completely flaccid. He was admitted to a local hospital where findings of a computed tomographic scan revealed low density in the periventricular white matter. Results of electroencephalography and cerebrospinal fluid tests were unremarkable. He was transferred to the intensive care unit of a university hospital, where he exhibited disconjugate gaze, bilateral anisocoria, and marked generalized hypotonia with preservation of reflexes. He was thought to have botulism and was transferred back to the local hospital and discharged with an apnea monitor. He began vomiting and required gavage feeding. No bowel movements were recorded for days. When the test results for botulism toxin were negative and his condition seemed to worsen, he was admitted to the University of California, Davis Medical Center.

He was lethargic and extremely hypotonic. There were no purposeful and few spontaneous movements. Deep tendon reflexes were very brisk, and there was clonus at the ankles. His eyes did not track. Petechiae were evident. Laboratory data included a leukocyte count of $2.4 \times 10^9/L$, a platelet count of $12 \times 10^9/L$, a hemoglobin level of 76 g/L, and a hematocrit of 0.22; differential cell counts were 0.06 for polymorphonuclear forms, 0.87 for lymphocytes, and 0.07 for monocytes. Leukocyte and platelet count nadirs were $1.3 \times 10^9/L$ and $3 \times 10^9/L$, respectively. The serum bicarbonate level was 24 mmol/L; sodium level, 130 mmol/L; potassium level, 4 mmol/L; and chloride level, 98 mmol/L. Urinalysis findings were positive for small ketones. A single test 1 month earlier had shown large ketones.

Analysis of the amino acids of the plasma revealed an elevated glycine concentration of 782 µmol/L. The urinary concentration was 1082 mmol per mole of creatinine; lysine values were also elevated at 260 mmol per mole of creatinine. Organic acid analysis revealed increased amounts of 3-hydroxypropioninate, propionylglycine, and methylcitrate (Table). The concentrations of lactate and 3-hydroxyisovalerate were 237 and 563 mmol per mole of creatinine, respectively. The plasma concentration of free carnitine was 6.6 µmol/L, and the esterified fraction was 16.0 µmol/L. The urinary free carnitine concentration was 9.2 mmol per mole of creatinine, and the esterified fraction was 130 mmol per mole of creatinine. A carboxylase assay of cultured fibroblasts revealed a deficiency of propionyl-CoA carboxylase: 25 and 18 pmol/min per milligram of protein for cases 1 and 2, respectively, vs 368 and 441 pmol/min per milligram in the respective simultaneous controls (laboratory control range, 338-570 pmol/min per milligram). Assay results of lymphocyte carboxylases were confirmatory: propionyl-CoA carboxylase activity was 24 pmol/min per milligram of protein, 10% of a simultaneous control. The blood concentration of ammonia was 165 µmol/L (231 µg/dL). The lactate level was 3.0 mmol/L; albumin level, 27 g/L. He was treated initially with parenteral glucose, water, and electrolytes. The albumin level fell to 18 g/L, and he developed edema, but the concentration of ammonia rose to 290 µmol/L (406 µg/dL) 3 days following admission and to 350 µmol/L (490 µg/dL) 2 days later. He had a generalized seizure. After treatment with parenteral carnitine and a low-protein diet, the hyper-

ammonemia resolved. Ammonia concentration was 37 µmol/L (52 µg/dL) 5 days later. By this time his pancytopenia had resolved, his weight had increased, and he had begun to have spontaneous movements, though he still required gavage feedings. The levels of organic acids had improved remarkably (Table). He never displayed acidosis, and the urine tested negative for ketones following the admission sample. Findings of magnetic resonance imaging scans revealed cerebral atrophy (Figure). Electroencephalographic examination revealed a background slow activity with transient multifocal spikes.

By age 7 years, the patient was wheelchair bound, hypotonic, and athetotic. His speech was dysarthric, and there were involuntary posturing and choreiform movements. He was preparing for the third grade in a regular classroom. By age 8 years, he had an overall score of 41 in the Terra Nova Assessment, just below the national average percentile of 50; his reading and language scores were in the average range, but mathematics and science were in the 35th and 14th percentiles, respectively. His head circumference was normal. A tonic neck response could be elicited. Deep tendon reflexes were exaggerated and plantar responses extensor. He had mild scoliosis.

RESULTS

In both patients, the findings of organic acid analysis of the urine were typical of those of propionic acidemia. In each patient, elevated levels of 3-hydroxypropionate and methylcitrate responded very well to reduced intake of protein and aggressive treatment with carnit-
tine. In case 1 there were no elevations of propionylglycine or tiglyl-glycine levels, while in case 2 the initial level of propionylglycine was higher than that of 3-hydroxypropionate. After 2 weeks of treatment, the level of tiglyl-glycine was still appreciably elevated. Six days later the level was 0, as was that of propionylglycine; the methylcitrate level was 80 mmol/mol of creatinine. With liberalization of the diet, levels of tiglylglycine and propionylglycine increased such that by age 1.5 years, the tiglyl-glycine level was 1059 mmol/mol of creatinine; propionylglycine, 111 mmol/mol of creatinine; and methylcitrate, 1014 mmol/mol of creatinine (Table).

Fibroblast assay results for propionyl-CoA carboxylase activity were 4% and 7% of simultaneous controls. Lymphocyte propionyl-CoA carboxylase activity in each was 5% of the control. These values are similar to those of patients presenting with typical acute neonatal ketoacidosis.\(^1\) In 10 such patients the mean fibroblast activity was 15 (range, 0-31) pmol/min per milligram of protein, and that of lymphocytes in 23 patients was 10 (range, 0-36) pmol/min per milligram of protein.

### COMMENT

The phenotypes of these 2 patients were strikingly similar and suggested severe involvement of the basal ganglia. The patient in case 1 developed global retardation of mental development, while in case 2 cognitive development was close to average in some spheres. Both patients had spastic quadriplegia and choreoathetosis. At first impression the neurologic picture of each resembled patients with Lesch-Nyhan disease.\(^7\) Furthermore, the patient in case 1 displayed self-mutilation of the lower lip that prompted an assay of hypoxanthine phosphoribosyltransferase activity. Contractures and overfolded ears in case 1 suggest Beals syndrome, but the folded ears of that disorder are quite different, and our patient’s contractures were acquired with his spasticity, not congenitally. Both patients had evidence of an abnormality in the basal ganglia revealed on magnetic resonance images, but their clinical presentations were much more spastic and choreoathetotic. Findings of neuropathologic examinations in a small number of patients who died after age 1 year have uniformly revealed lesions in the basal ganglia.\(^2,3,8-10\) One of our previously reported patients died of acute symmetric necrosis of the basal ganglia.\(^2\) The 2 patients in this report differed from that patient and the others in the absence of acute episodes of ketoacidosis. In neither case was an abnormal level of bicarbonate ever recorded. Our patient in case 2 had ketonuria observed on only 2 occasions despite many testings. These observations suggest that patients spared the alerting signal of ketoacidotic attacks may experience the indolent development of neuronal damage. Clearly, propionic acidemia has an effect on the central nervous system.

The pathogenesis of the cerebral and basal ganglia abnormalities is not clear. One factor is the hyperammonemia. In case 1, hyperammonemia was documented over a 3-week period in the hospital at age 15 years; there may well have been many such episodes. The patient in case 2 was hyperammonemic at the time of diagnosis and possibly before. The mechanisms for the development of hyperammonemia are consistent with experimental evidence that propionyl-CoA competitively inhibits N-acetylglutamate synthetase,\(^11\) which leads to inhibition of carbamylphosphate synthetase. This situation is unusual. Most patients with disorders of propionate metabolism manifest a developmental pattern\(^12\) in which most who develop hyperammonemia do so in the first episode of ketoacidosis and never again, or at least not after early infancy, and certainly not in the absence of ketoacidosis, as was documented in both cases in this study. In both patients, hyperammonemia resolved after treatment with carnitine and a low-protein diet, which is a strong argument for early diagnosis and treatment.

The activities of propionyl-CoA carboxylase were no different in these patients than they were in those presenting with the usual acute neonatal illness. The levels of organic acids in the urine in case 1 were diagnostic but not substantially elevated. The patient in case 2 had higher levels of propionylglycine and tiglyl-glycine than most patients. This pattern was also seen in the case of an 8-year-old girl we previously reported who died following infarction of the basal ganglia.\(^2\)

Propionic acidemia has been reported in 2 families of Amish ancestry in a single large Mennonite Amish kindred.\(^13\) Seven patients in that kindred had typical acute ketoacidotic episodes: 5 died in infancy, but 2 had seizure disorders without ketoacidosis (1 with mild mental retardation and the other with profound retardation, athetosis, and spastic quadriplegia). Patients in that kindred, like the patient in our case 1, were in the BC complementation group. Propionyl-CoA carboxylase is composed of an \(\alpha\) and a \(\beta\) subunit.\(^14,15\) Patients in complementation group A have mutations in the \(\alpha\) subunit, while those in group BC have mutations in the \(\beta\) subunit.

Neurologic sequelae reported\(^16\) in propionic acidemia have been more common in those surviving longer and have included pyramidal tract signs, severe chorea, and dystonia. An insidious onset of chronic progressive encephalopathy began with choreoathetosis following a respiratory tract infection in a 6-month-old infant who did not have ketoacidosis or hyperammonemia.\(^17\) This presentation is reminiscent of glutaryl-CoA dehydrogenase deficiency.

In an unusual case,\(^18\) a 31-year-old man was referred from a psychiatric hospital, where he had been admitted for confusion and bizarre behavior, because of the development of involuntary movements. His early motor and cognitive development had been delayed, and he had had episodes of vomiting and lethargy in infancy. On computed tomographic scan the basal ganglia appeared normal.

Experience with the patient in case 1 at age 15 years indicates that propionic acidemia should be added to those inborn errors of metabolism such as medium-chain acyl-CoA dehydrogenase deficiency and ornithine transcarbamylase deficiency\(^19,20\) that make up the differential diagnosis of Reye syndrome. This patient was hyperammonemic, hypoglycemic, and had elevation of transaminase activities in the blood. In addition, findings from
the histological examination of the liver revealed microvascular fat.

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