Propionic Acidemia: Unusual Course With Late Onset and Fatal Outcome

Thomas Lücke, Celia Pérez-Cerdá, Matthias Baumgartner, Brian Fowler, Stefanie Sander, Michael Sasse, Sabine Scholl, Magdalena Ugarte, and Anibh Martin Das

A 4½-year-old girl with a so far unremarkable medical history became comatose during a simple infection. She showed severe metabolic acidosis without elevation of lactate. In blood the branched-chain amino acids were increased. In urine ketone-bodies, increased 3-OH-isovaleric and 3-OH propionic acid excretion were detected, while methylmalonate was not found. The profile of acylcarnitines revealed increased propionylcarnitine. Despite restriction of protein supply, high-caloric nutrition, correction of acidosis, and supplementation of biotin and carnitine, the girl died 2 days after admission due to arrhythmia of the heart. In skin fibroblasts the activity of propionyl–coenzyme A carboxylase (PCC) was markedly decreased. Mutation analysis confirmed the diagnosis of propionic acidemia (PA) with compound heterozygosity for 2 new missense mutations L417W/Q293E in the PCCA gene, with the mother carrying the Q293E and the father the L417W mutation. Late-onset PA should be included in the differential diagnosis of unclear coma. Determination of the acylcarnitines using tandem mass spectrometry as well as organic acids in urine is recommended.

PROPIONIC ACIDEMIA (PA, MIM #606054; frequency ~1:50,000) is an autosomal recessive disorder caused by a defect of propionyl–coenzyme A carboxylase (PCC, EC 6.4.1.3). This biotin-dependent mitochondrial enzyme consists of 2 nonidentical subunits alpha and beta encoded by 2 genes: PCCA (MIM 232000) and PCCB (MIM 232050), respectively. The alpha subunit contains the biotin attachment site at the C-terminus and a biotin carboxylase domain. So far, 40 mutations have been found in the PCCA gene in patients with PA.[1] Some genotype-phenotype correlation seems to exist, with patients carrying null mutations in both alleles usually showing a severe clinical presentation.[2]

The main clinical findings are vomiting, lethargy, hypotonia, and metabolic ketoacidosis. In about 80% of the patients early clinical onset occurs during the neonatal period.[3] Propionate, 3 OH-propionate, and methylcitrate are typically increased in body fluids and serum carnitine is usually low. Hyperglycinemia (96%), hyperammonemia (88%), and hyperlysinemia (57%) may also be present.[3] Late-onset PA patients may show symptoms similar to those of patients with neonatal onset, such as recurrent episodes of vomiting, acidosis, and hyperammonemia, and they may develop muscular hypotonia and convulsions. The clinical picture of late-onset PA is more heterogenous,[4] and descriptions of fatal late-onset cases are rare.[5,6]. We describe an unusual case of late-onset PA with fatal outcome.

CASE REPORT

The 4½-year-old girl was the only child of an unrelated healthy German couple. Pregnancy, birth, and medical history were unremarkable. Her psychomotor development was normal. The patient had been referred to our outpatient emergency unit 4 weeks before the episode of decompensation described below, with purpura of both legs and arthritis. This episode was preceded by an upper respiratory tract infection. Platelet count and coagulation were normal. The skin rash was considered to be Henoch-Schönlein purpura, and after 1 to 2 weeks the rash disappeared spontaneously.

At the age of 4½ years she became comatose during a common upper airway infection. She showed a severe metabolic acidosis (pH 6.9; base excess [BE] −25.5 mmol/L, HCO_3 6 mmol/L, anion gap 27 mmol/L, lactate normal, glucose normal). Hyperammonemia of 198 μmol/L was found. Intoxication with ethylenglycol or methanol was excluded by gas chromatography–mass spectrometry (GCMS) and gas chromatography–flame ionization detection (GC-FID), respectively. Counts of leukocytes, especially neutrophils, hemoglobin, and thrombocytes in blood, CSF analysis, brain computed tomography scan, and echocardiography were normal. An electroencephalogram showed generalized delta activity. Branched-chain amino acids were markedly elevated, probably reflecting ketosis, while glycine and lysine were only slightly elevated.

In urine ketone bodies, an increased concentration of 3-OH isovaleric acid (630 mmol/mol creatinine; normal, <67) and a trace of 3-OH propionate were found by GCMS. The profile of acylcarnitines revealed an increased level of propionylcarnitine (11.9 μmol/L; normal, <3.5) by tandem mass spectrometry.

Despite restriction of protein supply, high-caloric nutrition, correction of acidosis, and supplementation of biotin (100 mg) and carnitine (100 mg/kg per day intravenously), the girl died 2 days after admission due to cardiac arrhythmia.

In skin fibroblasts propionate incorporation was reduced (1.91 nmol/mg protein in 16 hours; normal, 4.33 to 28.9). The activity of PCC (3 pmol/min per mg protein; normal, 287 to 2,150) was markedly decreased, while the activities of the other 2 mitochondrial carboxylases, pyruvate carboxylase and 3-methylcrotonyl CoA carboxylase, were in the normal range.

Mutation analysis revealed compound heterozygosity for 2 new missense mutations in the PCCA gene, L417W and Q293E. The mother carries the Q293E and the father the L417W mutation.

From the Department of Paediatrics, Hannover Medical School, Hannover, Germany; Centro de Diagnóstico de Enfermedades Moleculares, Facultad de Ciencias, Universidad Autónoma de Madrid, Madrid, Spain; Department of Paediatrics, University of Basel, Basel, Switzerland; and Screeninglab, Hannover, Germany.

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Address reprint requests to Thomas Lücke, MD, Department of Paediatrics, Hannover Medical School, Carl Neuberg Str. 1, D- 30625 Hannover, Germany.

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DISCUSSION

In about 80% of decribed PA patients, clinical onset occurs in the neonatal period with a classical clinical picture of vomiting, lethargy, neurologic symptoms, and keto-acidotic coma.[3,4] In these patients mortality is much higher than in the late-onset group.[7] The clinical and biochemical picture of late-onset PA is more heterogenous.[4] Late-onset PA patients are found to suffer from abnormal psychomotor development more often than early-onset PA patients and show mental and psychological disabilities.[4] In addition, patients with late-onset PA often show severe movement disorders.[7] Extrapyramidal symptoms such as dystonia or choreoathetosis were described in a 29-year-old man who presented with an adult-onset chorea[8] and even in PA patients without obvious acute episodes of metabolic decompensation.[9] These clinical findings are in line with neuroradiological[10] and neuropathological[11] observations showing a high frequency of basal ganglia lesions in late-onset PA patients.[10] A fatal acute basal ganglia infarction has been described in an 8-year-old girl with PA during metabolic decompensation.[5] Furthermore Pérez-Cerdá reported a 5-year-old boy with fatal necrosis of basal ganglia after a period of clinical deterioration.[6]

Pathophysiologically, an accumulation of toxic metabolites seems to impair mitochondrial energy production, especially in regions of the brain with a high rate of aerobic (mitochondrial) metabolism, such as basal ganglia.[12] "Metabolic decompensation" can be triggered by protein overload or febrile infections or prolonged fasting with accumulation of toxic substances.

Toxic substances have been shown to cause hyperammonemia in PA by inhibiting urea cycle enzymes.[13] Accumulation of 3-OH isovaleric acid in our patient is probably a secondary phenomenon, as well as due to a backflow of metabolites in the catabolic pathway of leucine caused by secondary inhibition of mitochondrial function and/or activation of alternative metabolic pathways.

The case reported here is unusual in that the medical history was unremarkable until the girl became comatose during an infection and died. Similar to the patient described by Pérez-Cerdá et al,[6] our patient had normal physical and psychomotor development until her fatal decompensation. In contrast, there was no evidence of basal ganglia damage either clinically or neuroradiologically despite severe metabolic acidosis and hyperammonemia, at least in the short term.

It remains unclear whether the purpura seen in this patient shortly before the acute decompensation was related to toxic metabolites accumulating in PA. In this context a so-called dermatitis acidemica has been reported in about 27% of PA cases.[3]

Some evidence for a genotype-phenotype correlation in PA exists since there is a tendency for null mutations to be related to the severe form and missense mutations to be related to the late-onset and mild forms of PA.[2] Interestingly, mutation analysis in our patient revealed compound heterozygosity for 2 new missense mutations. The boy with fatal late-onset PA published by Pérez-Cerdá et al was compound heterozygous for 2 mutations in the PCCB gene carrying a point mutation 1228 C→T on one allele and an in-frame 108-bp deletion on the other allele.[6] Unfortunately, more information on the nature of mutations in other cases with fatal late-onset PA is lacking in the literature.

CONCLUSION

Late-onset PA should be considered in cases of unclear coma. Determination of organic acids in urine and acylcarnitines in blood using tandem mass spectrometry is recommended. Phenotypic variability observed in late-onset PA is still not fully understood.

REFERENCES

1. Pérez B, Desviat LR, Rodríguez-Pombo P, et al: Propionic acidemia: Identification of twenty-four novel mutations in Europe and North America. Mol Gen Metabol 78:59-67, 2003

2. Pérez-Cerdá C, Merinero B, Rodríguez-Pombo P, et al: Potential relationsship between genotype and clinical outcome in propionic acidaemia patients. Eur J Hum Genet 8:187-194, 2000

3. Lehnert W, Sperl W, Suormala T, et al: Propionic acidaemia: Clinical, biochemical and therapeutical aspects. Eur J Pediatr 153:S68-S80, 1994 (suppl 1)

4. Van der Meer SB, Poggi F, Spada M, et al: Clinical outcome and long-term management of 17 patients with propionic acidemia. Eur J Pediatr 155:205-210, 1996

5. Haas RH, Marsden DL, Capistrano-Estrada S, et al: Acute basal ganglia infarction in propionic academia. J Child Neurol 10:18-22, 1995

6. Pérez-Cerdá C, Merinero B, Martí M, et al: An unusual late-onset case of propionic acidaemia: Biochemical investigations, neuroradiological findings and mutation analysis. Eur J Pediatr 157:50-52, 1998

7. Surtees RAH, Matthews EE, Leonard JV: Neurologic outcome of propionic acidemia. Pediatr Neurol 8:333-337, 1992

8. Sethi KD, Ray R, Roesel RA, et al: Adult-onset chorea and dementia with propionic acidemia. Neurology 39:1343-1345, 1989

9. Nyhan WL, Bay C, Beyer EW, et al: Neurologic nonmetabolic presentation of propionic academia. Arch Neurol 56:1143-1147, 1999

10. Bergman AJ, Van der Knaap MS, Smeitink JA, et al: Magnetic resonance imaging and spectroscopy of the brain in propionic acidemia: clinical and biochemical considerations. Pediatr Res 40:404-409, 1996

11. Hamilton RL, Haas RH, Nyhan WL, et al: Neuropathology of propionic acidaemia: A report of two patients with basal ganglia lesions. J Child Neurol 10:25-30, 1995

12. Matsuishi T, Stumpf DA, Chrislip K: The effect of malate on propionate mitochondrial toxicity. Biochem Med Metabol Biol 46:177-184, 1991

13. Glasgow AM, Chase HP: Effect of propionic acid on fatty acid oxidation and ureagenesis. Pediatr Res 10:683-686, 1976