

# Stroke-Like Episodes in Propionic Acidemia Caused by Central Focal Metabolic Decompensation

## Authors

S. Scholl-Bürgi<sup>1</sup>, E. Haberlandt<sup>1</sup>, T. Gotwald<sup>2</sup>, U. Albrecht<sup>1</sup>, S. Baumgartner Sigl<sup>1</sup>, M. Rauchenzauner<sup>1</sup>, K. Rostásy<sup>1</sup>, D. Karall<sup>1</sup>

## Affiliations

<sup>1</sup>Innsbruck Medical University Innsbruck, Department of Pediatrics IV, Division of Neuropediatrics and Inherited Metabolic Disorders, Innsbruck, Austria

<sup>2</sup>Innsbruck Medical University Innsbruck, Department of Radiology II, Innsbruck, Austria

## Key words

- propionic academia
- CSF/plasma ratio
- stroke-like episodes

## Abstract

Propionic acidemia caused by propionyl-CoA carboxylase deficiency frequently leads to neurologic complications. Herein we report an eleven-year-old patient with propionic acidemia having three stroke-like episodes during a period of 13 months characterized by acute reversible hemiplegia and vegetative symptoms like bradycardia or drowsiness. No biochemical signs of severe metabolic decompensation were detectable in plasma. At all three episodes, EEG was not indicative for status epilepticus, but in the acute episode it showed slowing of background activity emphasized on one side. MRI revealed reversible hyperintensities in cortical grey mat-

ter and basal ganglia. During the third episode a lumbar puncture was done in parallel with venous puncture. Concentrations of glutamine (902 μmol/L), glycine (24 μmol/L) and alanine (78 μmol/L) were elevated in CSF. In plasma glycine (1859 μmol/L) and alanine (608 μmol/L) concentrations were also elevated, whereas the glutamine (458 μmol/L) concentration was normal. CSF/plasma ratios were elevated for glutamine (1.97) and alanine (0.13) and normal for glycine (0.01). We assume that the stroke-like episodes in our patient may be caused by an acute focal cerebral metabolic decompensation, which is detectable by unspecific changes in MRI and by measuring amino acids and lactate in CSF versus plasma.

## Abbreviations

|       |                                     |
|-------|-------------------------------------|
| ▼     |                                     |
| BG    | basal ganglia                       |
| CNS   | central nervous system              |
| CRP   | C-reactive protein                  |
| CSF   | cerebrospinal fluid                 |
| FLAIR | fluid-attenuated inversion recovery |
| MRI   | magnetic resonance imaging          |
| MRS   | magnetic resonance spectroscopy     |
| PA    | propionic acidemia                  |

## Introduction

Propionic acidemia (PA, MIM 606054) is caused by a deficiency of propionyl-CoA carboxylase (PCC) (EC 6.4.1.3). PCC is a mitochondrial enzyme that catalyzes the ATP-dependent carboxylation of propionyl-CoA to d-methylmalonyl-CoA. Propionyl-CoA is produced by catabolism of the amino acids isoleucine, methionine, threonine, valine, the odd-chain fatty acids, the pyrimidines thymine and uracil and cholesterol [5].

Most patients with PA present in the newborn period with severe metabolic acidosis manifesting as feeding difficulties, episodic vomiting, lethargy and muscular hypotonia. Seizures, dehydration and hepatomegaly occur less frequently during the early period [16,25].

MRI in PA patients shows delayed myelination, cerebral atrophy with an enlarged ventricular system and subarachnoidal spaces and changes in the basal ganglia to a variable degree [2–4]. In MRS a decrease of *N*-acetylaspartate and *myo*-inositol and an elevation of glutamine/glutamate/GABA (Glx peak) in basal ganglia were detectable even in metabolically stable situations [2].

After the first derangement, the neurological outcome is often poor [22] and mental retardation to a varying degree is a common feature in PA, especially in patients with early onset of the disorder [15,22–24]. Additionally, the patients suffer from movement disorders without measurable changes in neurotransmitter concentrations in CSF [22] and seizures are reported frequently in PA patients [9,25]. Acute infantile hemiplegia after seizures was reported only in a

received 26.03.2009

accepted 19.06.2009

## Bibliography

DOI 10.1055/s-0029-1231065

Neuropediatrics 2009;

40: 76–81

© Georg Thieme Verlag KG

Stuttgart · New York

ISSN 0174-304X

## Correspondence

**Sabine Scholl-Bürgi, MD**

Medical University Innsbruck

Department of Pediatrics

Anichstraße 35

6020 Innsbruck

Austria

Tel.: +43/512/504 23 600

Fax: +43/512/504 25 886

sabine.scholl-buergi@uki.at

**Table 1** Clinical, EEG and MRI findings on three occasions in a PA patient with acute hemiplegia and vegetative symptoms.

| Episode                           | One   | Two  | Three   |
|-----------------------------------|---|--|---|
| age                               | 9 y 9 m   | 10 y 7 m   | 10 y 10 m   |
| weight (kg)                       | 31 (P50)  | 33 (P50)   | 33 (P25–50)   |
| height (m)                        | 1.31 (P10)                                      | 1.33 (P10)   | 1.34 (P3–10)  |
| therapy                           | protein defined nutrition                       | +  | +   |
|                                   | precursor free amino acid mixture               | 12 g per day   | 12 g per day  |
|                                   | L-carnitine (mg per day)                        | 2 000  | 2 000   |
|                                   | medication                                      | levetiracetam therapy (start)  | levetiracetam (30 mg per kg bw)   |
| symptoms                          | drowsiness, vomiting, weakness left arm and leg | drowsiness, weakness left side, bradycardia  | drowsiness, low temperature, one week before: weakness of right side                    |
| MRI                               | <b>day two</b>                                  | <b>control (three weeks later)</b>   | <b>day one</b>  |
| diffusion                         | positive  | normal   | slightly positive   |
| PD/T <sub>2</sub> -weighted       | cortical positive, BG positive                  | cortical normal, BG slightly positive  | cortical normal, BG slightly positive   |
| FLAIR                             | cortical positive, BG positive                  | cortical normal, BG slightly positive  | cortical normal, BG slightly positive   |
| T <sub>1</sub> -weighted – / + Gd | normal  | normal   | normal  |
| MR angiogram                      | normal  | normal   | Normal  |
| spectroscopy                      | not available                                   | not available  | not available   |
| EEG                               | <b>day two</b>                                  | <b>day three</b>   | <b>day one</b>  |
| background activity               | coma activity (predominantly on the right side) | right side 3–4/s, left side 5–7/s (wake), right side 2–3/s, left side 5/s (drowsiness) | both sides 8–10/s (wake), right side 3/s, left side 1–1.5/s (drowsiness)                |
| epileptiform discharges           | not detectable                                  | spike-waves temporo-parieto-occipital on both sides with secondary generalization      | spikes and spike-slow-wave 3/s on the left side occipital and on the right side central |

ten-month-old girl with PA. The hemiplegia lasted for three months [19].

We report an eleven-year-old female patient with propionic acidemia who had three episodes with acute hemiparesis and vegetative symptoms like drowsiness and bradycardia within a period of 13 months.

### Patient and Methods

The patient is an Austrian girl in whom clinical symptoms began at age 3 days with tachypnea, feeding difficulties and lethargy. Diagnosis was established at age 5 days by determination of organic acid excretion in urine. Propionyl-CoA carboxylase activity was reduced and the diagnosis was later confirmed by demonstration of homozygosity for the mutation IVS 11-2A>G in the PCCB gene of propionyl-CoA carboxylase [14]. She was treated with a protein-defined diet (actually 1.3 g/kg/d) supplemented with L-carnitine and an amino acid preparation excluding methionine, threonine, valine and isoleucine (Table 1). Between ages 9 and 10 years she had three stroke-like episodes without apparent metabolic decompensation.

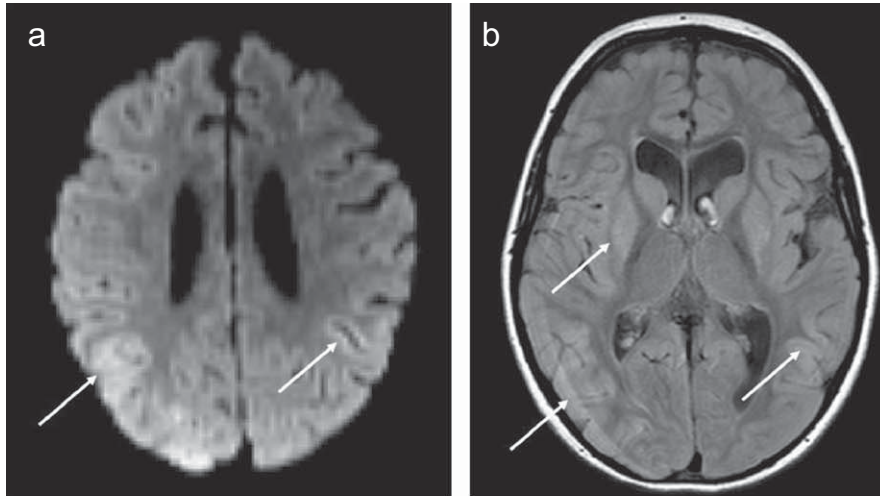
At the first episode the patient was 9 years and 9 months old, clinical symptoms were sudden onset of drowsiness, vomiting and weakness of the left arm and leg. There was no infection detectable and no signs of catabolism. Routine laboratory results showed only slightly elevated ammonia and lactate concentrations and were otherwise normal (including CSF results, Table 2).

Plasma amino acid analysis showed elevated concentrations of proline, glycine, alanine and lysine and decreased concentrations of isoleucine (Table 3). A CT scan was normal (on day one), a cerebral MRI scan at day two of hospitalization showed slightly hyperintense basal ganglia on both sides and hyperintense cortical grey matter on the right temporal side on diffusion and FLAIR imaging sequences (Table 1, Figs. 1a, b). A control MRI three weeks later showed an improvement of the previous findings (Table 1, Figs. 1c, d). EEG was done on day two of hospitalization (conducted under general anaesthesia for MRI scan) and showed slowing of background activity emphasized on the right side (Table 1, Fig. 2a). Later in the course, spike-waves on the central area on the left side were detectable (Fig. 2b). Therefore, therapy with levetiracetam (with increasing dose of 30 mg per kg body weight) was started because a possible non-convulsive status or seizure could not be ruled out at that time.

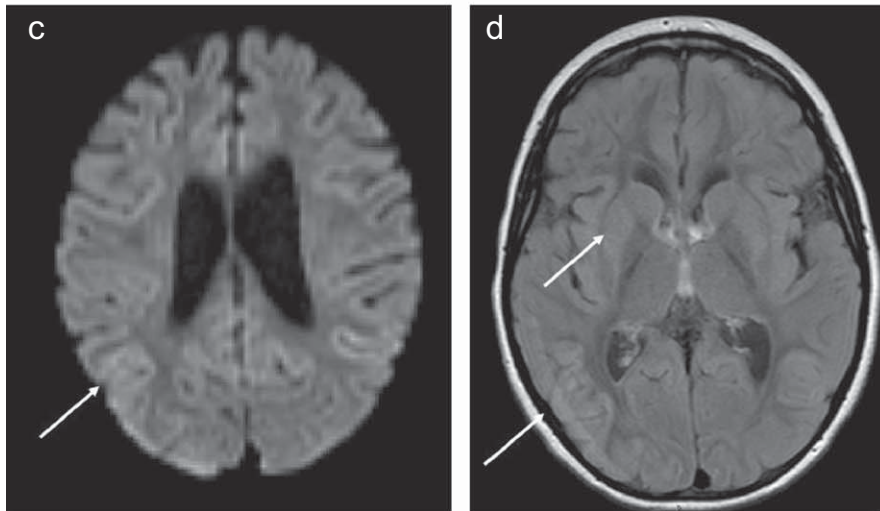
At age 10 years and 7 months she again developed an acute hemiparesis of the left side, drowsiness, had a bradycardia (down to 40/min) and low body temperature (35.7 °C). Routine laboratory results on admission were normal (Table 2). Plasma amino acid analysis showed elevated proline, glycine and alanine concentrations (Table 3). In EEG on day three a slowing especially of the right side and spike waves temporo-parieto-occipital on both sides were detectable (Table 1). A cerebral MRI scan was not performed.

One week before the last admission to hospital, at age 10 years and 10 months, the patient had vegetative symptoms like low

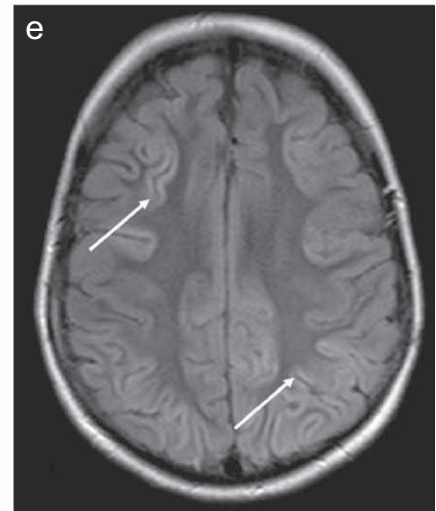
## episode one, day two



## episode one, control



## episode three, day one



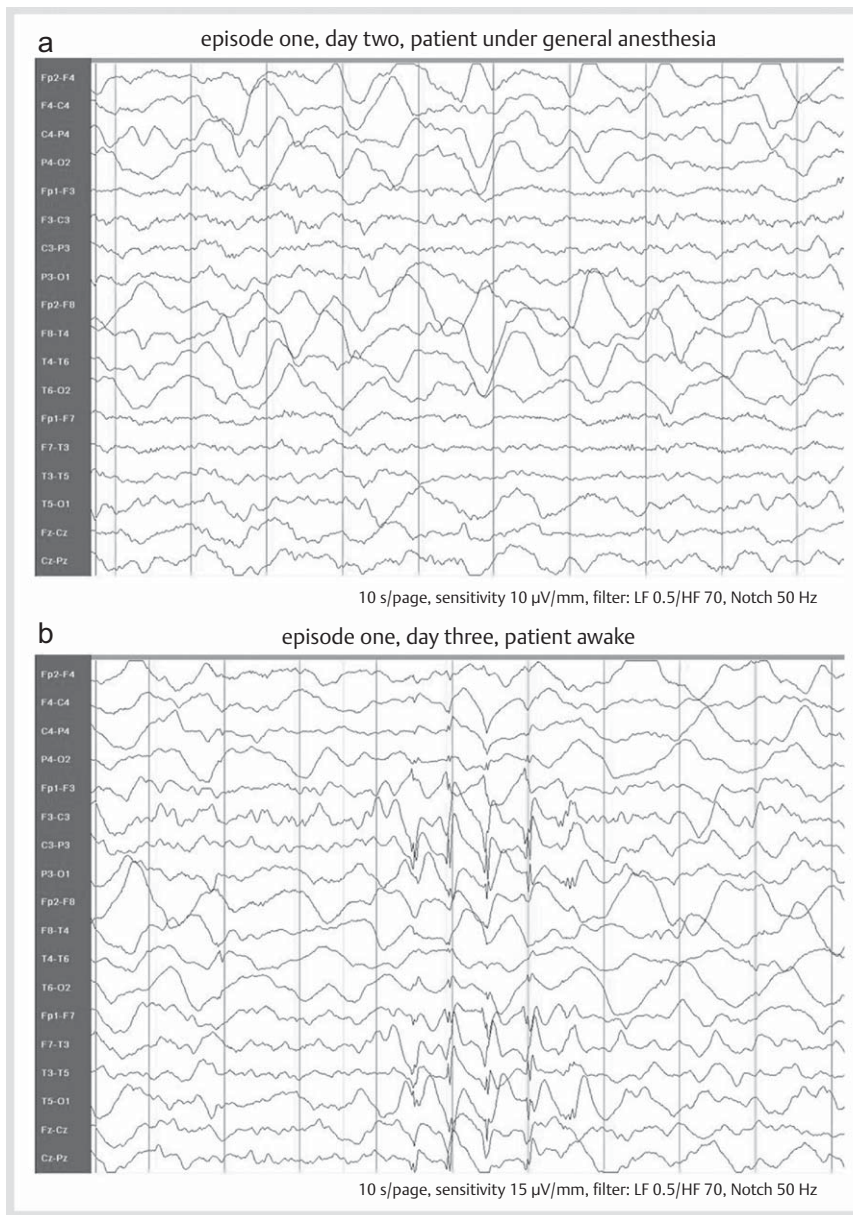
**Fig. 1** MRI scans at episode one and three (diffusion and FLAIR imaging) showing abnormal hyperintense signal of cortex and basal ganglia. Diffusion (a) and FLAIR (b) imaging, abnormal hyperintense signal of cortex and basal ganglia (arrows). Diffusion (c) and FLAIR (d) imaging, normalization of hyperintense signal of cortex and basal ganglia (arrows). FLAIR imaging (e), abnormal hyperintense signal of cortex (arrows).

body temperature and paleness and additionally weakness of the right side twice. These symptoms lasted for a maximum of two hours. On the day of last admission to hospital the mother reported that the girl suddenly became pale, was whining and laid down. The body temperature was low ( $35.7^{\circ}\text{C}$ ) and subsequently she vomited once. On admission (at 2 pm) ammonia concentration in plasma was slightly elevated ( $196\mu\text{mol/L}$ ), whereas the other routine laboratory results were again normal including blood gas analysis (Table 2). In the evening a lumbar puncture was done (at 8 pm). The patient had her last meal more than six hours before, but was receiving glucose infusion ( $6\text{ g/kg b.w. per day}$ ). In CSF, an elevated lactate concentration ( $5.2\text{ mmol/L}$ ) was detectable (Table 2). Amino acid concentrations in plasma and CSF are shown in Table 3 (note: CSF was free of erythrocytes). EEG again showed slowing of background activity emphasized of the left side and temporo-parieto-occipital spike-waves on both sides accentuated on the right side (Table 1, Figs. 2c, d). An MRI scan showed hyperintense cortical grey matter in FLAIR imaging and slightly hyperintense

basal ganglia on both sides (Table 1, Fig. 1e). Clinical symptoms resolved completely within the next day without a specific therapy.

### Discussion

Our patient had three episodes of acute hemiplegia and vegetative symptoms like bradycardia, low body temperature and drowsiness. These episodes can be interpreted as stroke-like episodes. Despite frequent reports on neurological outcome in PA patients, acute hemiplegia or stroke-like episodes are rarely reported. Stroke-like episodes are focal cerebral disturbances not primarily due to a vascular insufficiency, resulting in a focal neurological deficit that is persistent but can also recover [12]. They can occur in mitochondriopathies [13] and other inborn errors of metabolism [21]. Mechanisms for stroke-like episodes with focal neurological signs, beside others, include perfusion abnormalities and accumulation of toxic metabolites [21].

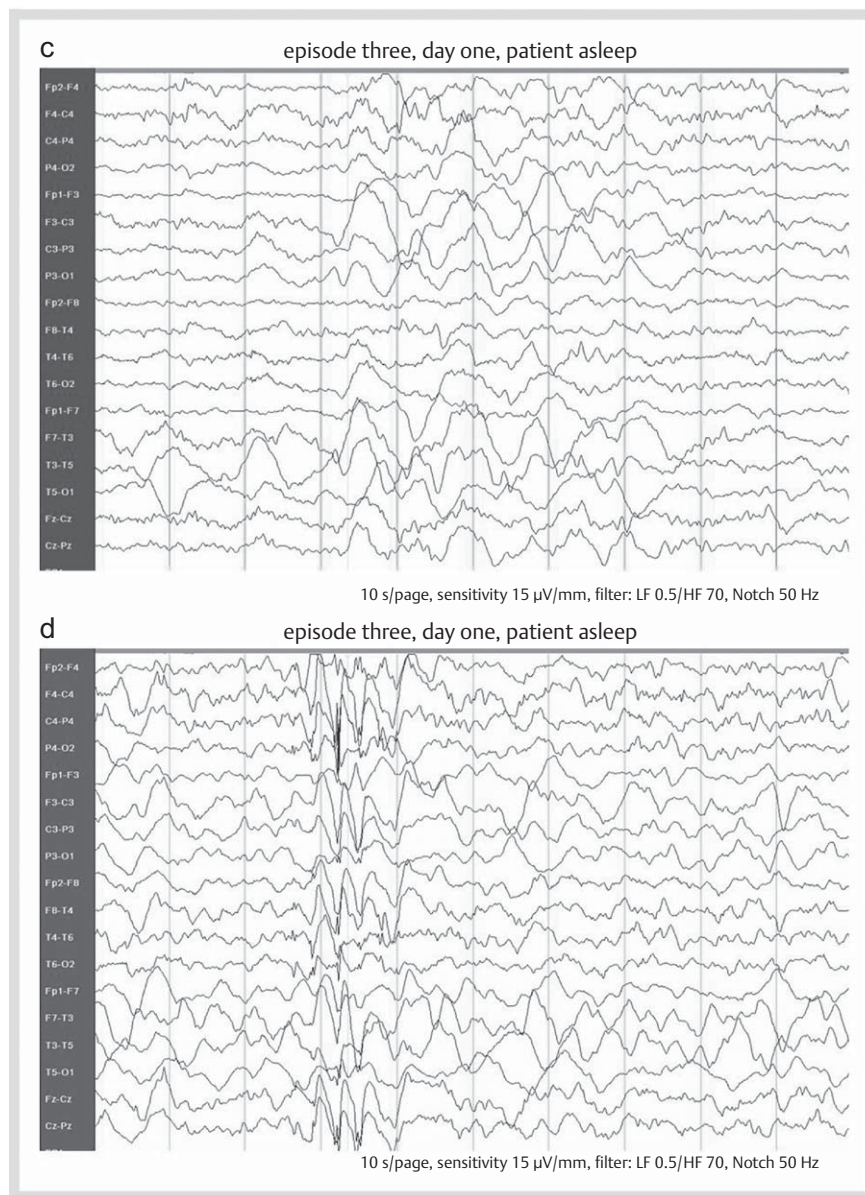


**Fig. 2** EEG investigations **a**: slowing of background activity emphasized on the right side; **b**: slowing of background activity emphasized on the right side, spike-waves central area left side with tendency of generalization.

In our patient severe metabolic decompensation was not detectable in plasma. MRI showed discrete changes of cortical grey matter on one side and additional changes in basal ganglia on both sides. EEG showed asymmetric slowing of background activity indicating focal metabolic changes. In the third episode a lumbar puncture was done in parallel with venous puncture. Interestingly, glutamine and lactate concentrations in plasma were normal, but in CSF elevated. Consequently, the CSF/plasma ratios of these metabolites were elevated. Additionally, alanine concentrations in CSF and plasma and CSF/plasma ratio were slightly elevated, whereas glycine concentrations were elevated in CSF and plasma, but not CSF/plasma ratio – as has already been shown in other PA patients [17]. The elevation of alanine, lactate and glutamine concentrations in CSF indicate cerebral production and trapping of metabolites as a cause (or result) of neurological symptoms. In addition, Kölker et al. [10] hypothesized that the limited efflux of dicarboxylic acids produced in CNS of patients with organic acidurias leads to neurological symptoms. We showed that in our patient this is true even for secondary elevated metabolites like alanine, lactate and

glutamine, where the elevated CSF/plasma ratios indicate trapping in CNS. This is a hint at significant stress-induced amino acid catabolism in the brain caused by cerebral production of organic acids as hypothesized by Morris [11].

Interestingly, plasma glutamine concentrations in PA patients are normal even during hyperammonemia [6]. This may be caused by “inability to maintain adequate levels of glutamine precursors through a dysfunctional Krebs cycle” [6]. In metabolically stable situations, CSF glutamine concentrations can be normal, but in MRS the Glx peak (glutamine, glutamate and some GABA) in brain tissue is elevated [2]. Glutamine can be synthesized from glutamate and ammonia catalyzed by glutamine synthetase, an astroglia-specific enzyme. Glutamine is a non-toxic ammonia carrier within the CNS and additionally it is an idiogenic osmolyte leading to astrocytic swelling [1]. Mechanisms which lead to glutamine synthesis in CNS in our patient are unclear, as ammonia in plasma was not massively elevated at the time of admission. However, one could speculate that this was the case before admission and therapy with the “at



**Fig. 2** (Continued) **c**: slowing of background activity emphasized on the left side; **d**: slowing of background activity emphasized on the left side, spike-waves on the occipital area of the right side with generalization.

**Table 2** Laboratory findings on three occasions in a PA patient with acute hemiplegia and/or vegetative symptoms.

| Episode                   | One                                     | Two      | Three     |         |
|---------------------------|---|----------|-----------|---------|
| age                       | 9 y 9 m                                 | 10 y 7 m | 10 y 10 m |         |
| laboratory investigations | day one                                 | day one  | day one   |         |
| blood                     | urea (mmol/L)                           | 3.3      | 4.8       | 3.2     |
|                           | creatinine ( $\mu\text{mol}/\text{L}$ ) | 26       | 25        | 36      |
|                           | GOT (U/L)                               | 18       | 45        | 32      |
|                           | GPT (U/L)                               | 17       | 26        | 17      |
|                           | blood gases                             | pH 7.38  | pH 7.32   | pH 7.43 |
|                           | ammonia ( $\mu\text{mol}/\text{L}$ )    | 92       | 70        | 196     |
|                           | lactate (mmol/L)                        | 4.2      | 2.4       | 2.1     |
|                           | leukocytes (per $\mu\text{L}$ )         | 4900     | 4600      | 5800    |
|                           | hemoglobin (mmol/L)                     | 70.1     | 79.4      | 73.8    |
|                           | thrombocytes (per $\mu\text{L}$ )       | 105 000  | 86 000    | 129 000 |
| CSF                       | CRP (mg/L)                              | 10.7     | 4.7       | 8.7     |
|                           | leukocytes (per $\mu\text{L}$ )         | 0        |           | 0       |
|                           | protein (mg/L)                          | 271      |           | 215     |
|                           | glucose (mmol/L)                        | 4.7      |           | 3.8     |
|                           | lactate (mmol/L)                        | n. d.    |           | 5.2     |

(n. d. = not determined)

**Table 3** Amino acid concentrations in plasma and CSF and CSF/plasma ratio in a PA patient with reference values in brackets (amino acid concentrations were determined as previously described [18], values in bold elevated concentrations, cursive decreased values; plasma reference values are indicated only once, for plasma reference values see [8,20], for CSF reference values see [7,20] (\* reference value for CSF proline is taken from [18]) and for CSF/plasma ratios see [18] (CSF/plasma ratio glutamate is not available, n.a.))

|               | episode one<br>day one<br>plasma (µmol/L) | episode two<br>day three<br>plasma (µmol/L) | plasma (µmol/L)        | episode three<br>day one<br>CSF (µmol/L) | CSF/plasma ratio        |
|---------------|---|---|------------------------|--|-------------------------|
| glutamine     | 355                                       | <b>317</b>                                  | 458 (333–809)          | <b>902</b> (334–658)                     | <b>1.97</b> (0.57–1.28) |
| glutamate     | 18  | 56  | <b>96</b> (14–78)      | 0.3 (<8.3)                               | 0.00 (n.a.)             |
| proline       | 245                                       | 256   | <b>566</b> (40–332)    | 3 (1.5–7.9)*                             | 0.01 (0.01–0.06)        |
| glycine       | <b>1 178</b>                              | <b>1 217</b>                                | <b>1 859</b> (107–343) | <b>24</b> (2.9–7.9)                      | 0.01 (0.00–0.05)        |
| alanine       | 541                                       | 357   | <b>608</b> (120–600)   | <b>78</b> (11.1–29.6)                    | <b>0.13</b> (0.04–0.13) |
| valine        | <b>52</b>                                 | <b>97</b>                                   | <b>124</b> (132–480)   | 8 (7.6–18.0)                             | 0.06 (0.05–0.11)        |
| isoleucine    | 19  | 42  | 52 (6–122)             | <b>2</b> (2.2–6.2)                       | 0.04 (0.03–0.11)        |
| leucine       | 68  | 76  | 178 (30–246)           | <b>20</b> (5.4–15.4)                     | 0.11 (0.08–0.18)        |
| tyrosine      | 59  | 45  | <b>126</b> (19–119)    | <b>27</b> (4.3–11.7)                     | 0.22 (0.13–0.30)        |
| phenylalanine | 62  | 34  | 88 (26–98)             | <b>23</b> (0.5–15.9)                     | 0.26 (0.12–0.28)        |
| lysine        | 189                                       | 256   | <b>455</b> (66–270)    | <b>62</b> (9.1–25.5)                     | 0.14 (0.09–0.33)        |
| arginine      | 43  | 38  | 96 (12–112)            | 19 (11.3–29.5)                           | 0.20 (0.00–0.75)        |

home unwell-regime” was successful in decreasing ammonia levels in the periphery but not in the CNS.

Metabolites like alanine and lactate indicate that brain energy metabolism – especially oxidative phosphorylation – is disturbed. Alanine can be synthesized from pyruvate by accepting an amino group from glutamate by an alanine aminotransferase reaction. Pyruvate can additionally be reduced to lactate by accepting electrons from NADH.

We assume that the stroke-like episodes in our patient may be caused by an acute focal cerebral metabolic decompensation, which causes detectable unspecific changes in MRI and can be demonstrated by measuring amino acids and lactate in CSF versus plasma. We conclude that these investigations are useful for the diagnosis of stroke-like episodes in patients with inborn disorders of metabolism.

## References

- Albrecht J, Dolińska M. Glutamine as a pathogenic factor in hepatic encephalopathy. *J Neurosci Res* 2001; 65: 1–5
- Bergmann AJW, Van der Knaap MS, Smeitink JAM et al. Magnetic resonance imaging and spectroscopy of the brain in propionic acidemia: clinical and biochemical considerations. *Ped Res* 1996; 40: 404–409
- Brismar J, Ozand PT. CT and MR of the brain in disorders of propionate and methylmalonate metabolism. *AJNR* 1994; 15: 1459–1473
- Chemelli AP, Schocke M, Sperl W et al. Neonatal-onset propionic acidemia: neurologic and developmental profiles, and implications for management. *J Magn Reson Imag* 2000; 11: 596–600
- Fenton WA, Gravel RA, Rosenberg DS. Disorders of propionate and methylmalonate metabolism. In: Scriver CR, Beaudet AL, Sly W, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*. 8<sup>th</sup> edn. New York: McGraw-Hill; 2001; 2165–2190
- Filipowicz HR, Ernst SL, Ashurst CL et al. Metabolic changes associated with hyperammonemia in patients with propionic acidemia. *Mol Gen Metab* 2006; 88: 123–130
- Gerrits GP, Trijbels FJ, Monnens LA et al. Reference values for amino acids in cerebrospinal fluid of children determined using ion-exchange chromatography with fluorimetric detection. *Clin Chim Acta* 1989; 182: 271–280
- Gregory DM, Sovetts D, Clow CL et al. Plasma free amino acid values in normal children and adolescents. *Metabolism* 1986; 35: 967–969
- Haberlandt E, Trinka E, Zimmerhackl LB et al. EEG-alterations in patients with propionic acidemia. *Neuropediatrics* 2004; 35: 84
- Kölker S, Sauer SW, Surtees RA et al. The aetiology of neurological complications of organic acidemias—a role for the blood-brain barrier. *J Inherit Metab Dis* 2006; 29: 701–704
- Morris AAM. Commentary on: The aetiology of neurological complications of organic acidemias – a role for the blood-brain barrier Kölker S, Sauer SW Surtees RA, Leonard JV. *J Inherit Metab Dis* 2006; 29: 705–706
- Pavlikis SG, Kingsley PB, Bialer MG. Stroke in children: genetic and metabolic issues. *J Child Neurol* 2000; 15: 308–315
- Pavlikis SG, Phillips PC, DiMauro S et al. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes: a distinctive clinical syndrome. *Ann Neurol* 1984; 16: 481–488
- Pérez B, Desviat LR, Rodríguez-Pombo P et al. Propionic acidemia: identification of twenty-four novel mutations in Europe and North America. *Mol Genet Metab* 2003; 78: 59–67
- Pérez-Cerdá C, Merinero B, Rodríguez-Pombo P et al. Potential relationship between genotype and clinical outcome in propionic acidemia patients. *Eur J Hum Genet* 2000; 8: 187–194
- Sass JO, Hofmann M, Skladal D et al. Propionic acidemia revisited – A workshop report. *Clin Pediatr* 2004; 43: 837–843
- Scholl-Bürgi S, Korman SH, Applegarth DA et al. The relation of cerebrospinal fluid and plasma glycine levels in propionic acidemia, a 'ketotic hyperglycinaemia'. *J Inherit Metab Dis* 2008; 31: 395–398
- Scholl-Bürgi S, Haberlandt E, Heinz-Erian P et al. Determination of amino acid CSF/plasma-ratios by ion-exchange chromatography with ninhydrin-detection in children: influence of age and usefulness for clinical purposes. *Pediatrics* 2008; 121: e920–926
- Shigematsu Y, Mori I, Nakai A et al. Acute infantile hemiplegia in a patient with propionic acidemia. *Eur J Pediatr* 1990; 149: 659–660
- Shih VE. Amino acid analysis In: Blau N, Duran M, Blaskovic ME, Gibson KM, eds. *Physician's guide to the laboratory diagnosis of metabolic diseases*. 2<sup>nd</sup> edn. Berlin, Heidelberg, New York: Springer; 2003; 11–26
- Sperl W, Felber S, Skladal D et al. Metabolic stroke in carbamyl phosphate synthetase deficiency. *Neuropediatrics* 1997; 28: 229–234
- Surtees RAH, Matthews EE, Leonard JV et al. Neurologic outcome of propionic acidemia. *Pediatr Neurol* 1992; 8: 333–337
- Touati G, Valayannopoulos V, Mention K et al. Methylmalonic and propionic acidurias: Management without or with a few supplements of specific amino acid mixture. *J Inherit Metab Dis* 2006; 29: 288–298
- 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* 1996; 155: 205–210
- Wolf B, Hsia YE, Sweetman L et al. Propionic acidemia: A clinical update. *J Pediatr* 1981; 99: 835–846