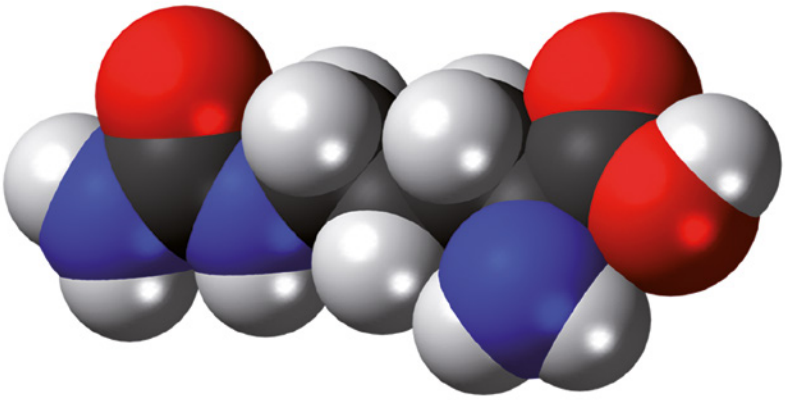
SWISS SOCIETY OF NEONATOLOGY

Winner of the Case of the Year Award 2014

# Neonatal presentation of citrullinemia

May 2014



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## INTRODUCTION

Severe hyperammonemia in a newborn is an uncommon problem, which is typically revealed by symptoms of encephalopathy that may include seizures. Etiologies include sepsis, severe liver failure and inborn errors of metabolism, mainly urea cycle disorders, but also organic acidurias, fatty acid oxidation disorders and several others.

## CASE REPORT

This male infant was born by normal vaginal delivery to a 27-year-old G2/P1 at 38 4/7 weeks of gestation after an uneventful pregnancy. No risks for infection were recorded. Umbilical arterial cord-pH was 7.26, Apgar scores 9, 10 and 10 at 1, 5 and 10 minutes, respectively. Birth weight was 3300 g (P50), length 51 cm (P25-50) and head circumference 35.5 cm (P50).

The infant was breastfed in the delivery room and showed vigorous sucking. However, after transfer to the maternity ward, the mother expressed concerns as the child consistently refused to feed and regurgitated abundantly. On day 3 of life, the infant appeared increasingly lethargic before developing a sudden episode of generalized hypertonia with deviation of the eyes to the right during a few seconds. A similar episode, 2 hours later, was accompanied by clonus of the right arm. On neurological examination, the fontanel and pupils appeared normal, but lethargy, axial hypotonia, peripheral hypertonia particularly of the right arm, an enhanced grasping reflex and diminished su-

cking reflex were observed. Blood gases, glucose and electrolytes values were normal.

The encephalopathic infant was transferred to the NICU for further work-up and treatment of suspected convulsions. Phenobarbital was started and the patient was intubated due to a rapidly progressive comatose state. Antibiotic and antiviral coverage were initiated. Laboratory exams included a complete blood count, C-reactive protein and blood chemistry. All came back within their reference range, except for marked hyperammonemia at 688 µmol/l 70 hours after birth and an increased lactate concentration of 4.8 mmol/l.

As there was no acidosis and no evidence of an infection or liver failure, a urea cycle disorder was strongly suspected. Ammonia increased to a maximal value of 1164 µmol/l 3 hours later, while ammonia-scavenging therapy was commenced. A loading dose of intravenous sodium benzoate and arginine were started. The patient was sent to the operating room for insertion of a hemodiafiltration catheter. After 24 hours of hemodiafiltration with concurrent administration of glucose, sodium benzoate and arginine, ammonia levels stabilized below 200 µmol/l. At that time, metabolic laboratory results revealed markedly increased plasma citrulline of 2090 µmol/l, glutamine of 1286 µmol/l and decreased ornithine levels of 29 µmol/l, consistent with a deficiency of argininosuccinate synthase (citrullinemia type 1). An EEG recorded 2 days after

the first convulsions showed isolated multifocal temporal spikes without further clinical seizures.

After three days in a deep coma, the baby recovered slowly and displayed an almost normal neurological exam one week later. In parallel, nasogastric tube feeding was progressively weaned to oral feeding. Treatment consisted of a protein-controlled diet, the ammonium-scavenging drug sodium benzoate and arginine. The amount of protein and essential amino acids in the diet and medication dosages were adjusted according to his clinical condition, weight and ammonia and amino acid profiles. Phenobarbital was tapered off over 25 days.

Brain MRI on day 7 showed diffuse white matter abnormalities, multiple ischemic-hemorrhagic lesions and bilateral restriction of the diffusion coefficient in the globus pallidus, the splenium of the corpus callosum, the periinsular and perirolandic cortex (Fig. 1). Follow-up MRI performed two weeks later confirmed the diffuse white matter abnormalities, and showed bilateral symmetric globus pallidus abnormal signal intensity and bilateral cortical laminar necrosis at the level of the central sulcus (Fig. 2). The infant was discharged home at 5 weeks of age in good general health, albeit yet with a slightly abnormal neurological exam displaying enhanced sensitivity to noise and increased patellar reflexes.

Up to his current age of 9 months, he did not experience any metabolic decompensation, and demonstrated normal weight gain, height and head growth. Neurodevelopmental assessment was performed at 3 months: the infant appeared alert, with good social interactions, but displayed a limited range of spontaneous movements with atypical postures, a tendency to keep his fists clenched, a persistent marked asymmetric tonic neck reflex, axial hypotonia and peripheral hypertonia. On the Baley-II Scales of Infant Development, his scores were within the range of moderately delayed psychomotor development. On follow-up at 9 months, he appeared cheerful, with good eye contact, visual exploration and tracking; however, he did not reach for objects, had not started babbling and could not yet sit unsupported. In addition to his marked psychomotor delay, he displayed early signs of possible dystonic cerebral palsy with intermittent decreases in axial tonus, associated with hypertonia and athetosis of the extremities.

## DISCUSSION

The differential diagnosis of encephalopathy and/or seizures in a newborn is broad; therefore, a few key points should be kept in mind. Is it a term infant? Was delivery uneventful? Did symptoms occur after a symptom-free interval of more than 12-24 hours? What are the results of the baseline laboratory work-up? Clues to the initial differential diagnosis are listed in the table.

The onset of neurological symptoms after a symptom-free interval of more than 12-24 hours following a normal delivery with normal Apgar scores renders hypoxic-ischemic encephalopathy unlikely. Neonatal arterial ischemic stroke may also present with delayed focal seizures but in general with normal alertness up to the event and in between seizures. Neonatal cerebral sinus venous thrombosis might be associated with non-specific signs and profound lethargy. Sepsis may obviously also be associated with progressive encephalopathy: a sepsis work-up is generally warranted and antimicrobial therapy should be started while waiting for laboratory results. The key features of increasingly poor feeding, vomiting and progressive lethargy with or without seizures should quickly direct towards a metabolic origin. Hence, whenever performing blood gas analysis or a sepsis work-up in a newborn aged 2 to 7 days of age with signs of progressive encephalopathy, measurement of serum ammonia concentration should be included (1).

Initial investigations in our patient included a full blood count, blood gas analysis, liver and renal function tests, rapidly followed by a plasma amino acid profile, urinary organic acid, cerebral ultrasound and, after clinical stabilization, brain MRI. The infant had highly elevated serum ammonia levels associated with normal serum glucose and anion gap suggestive of a urea cycle defect.

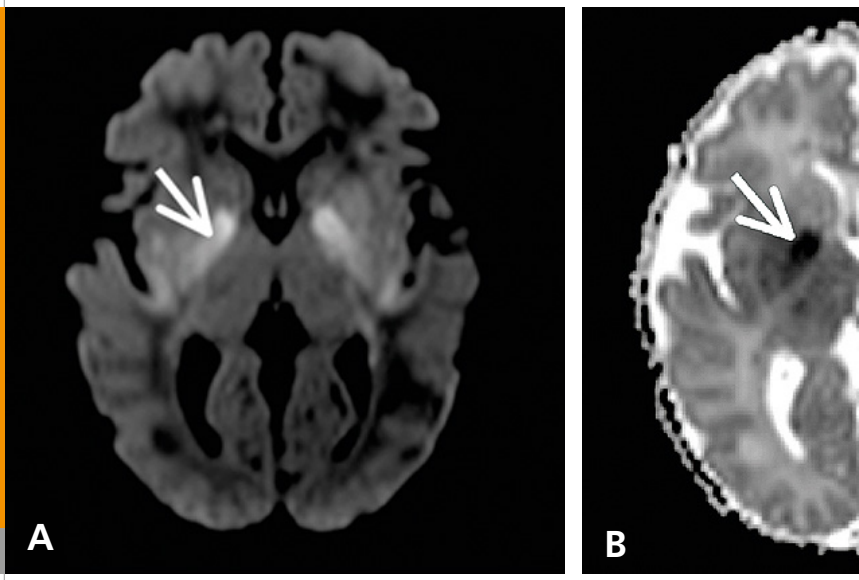
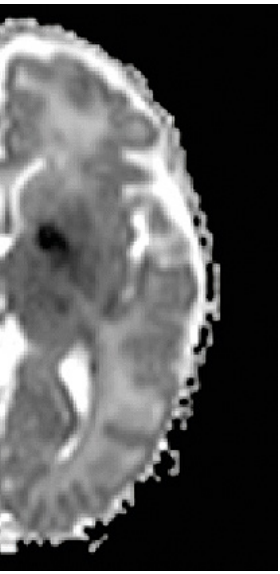
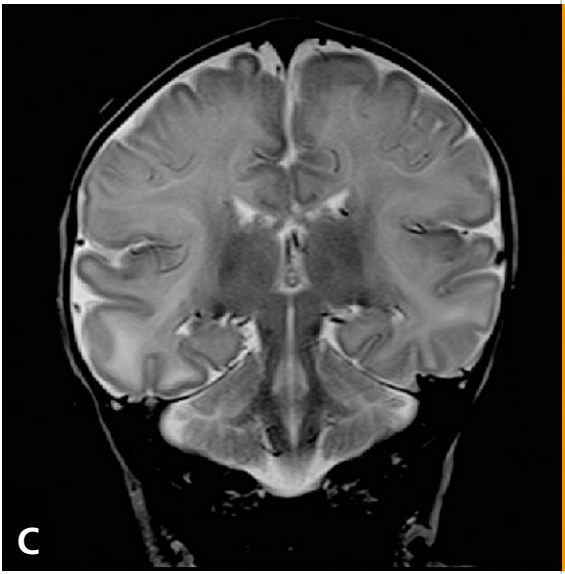



Fig. 1

*First MRI (4 days after onset of symptoms): A) DWI and B) ADC map: bilateral symmetric globus pallidus restricted diffusion (white arrow); C) T2WI: diffuse white matter signal abnormality.*

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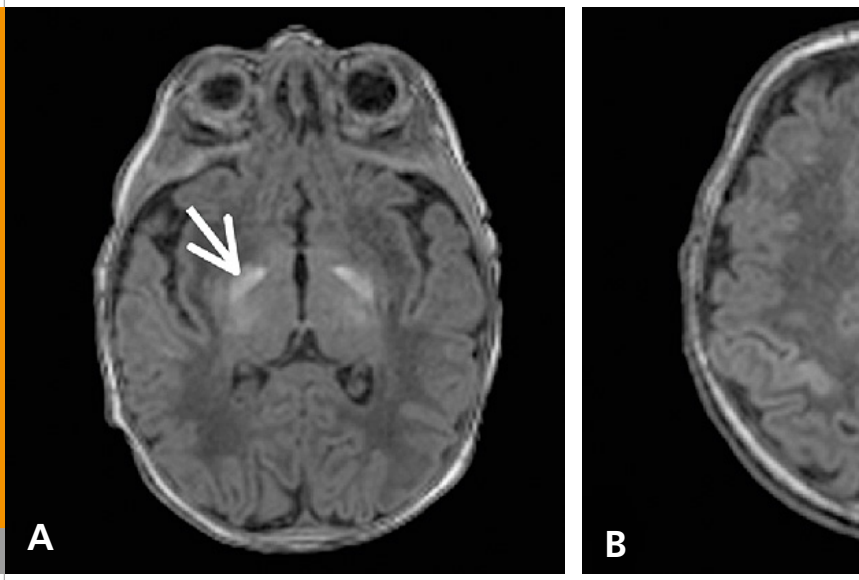
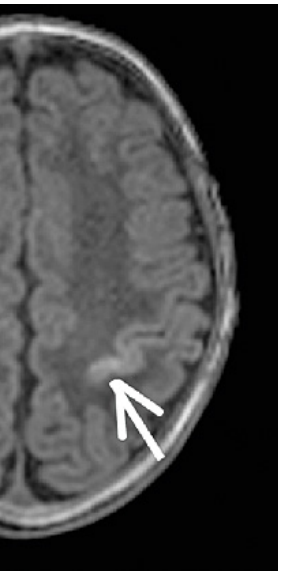



Fig.2

*Follow-up MRI (2 weeks after the first MRI): A) T1WI: bilateral globus pallidus hyperintensity (white arrow); B) T1WI: bilateral central sulcus hyper-intensity compatible with cortical laminar necrosis (white arrow); C) T2 WI: pronounced diffuse white matter signal abnormalities*

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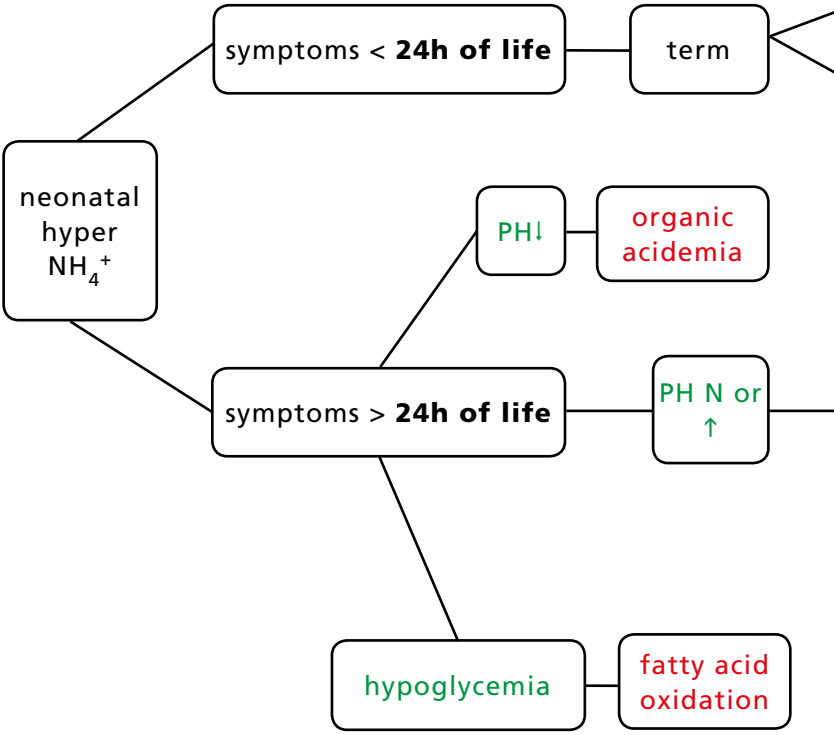
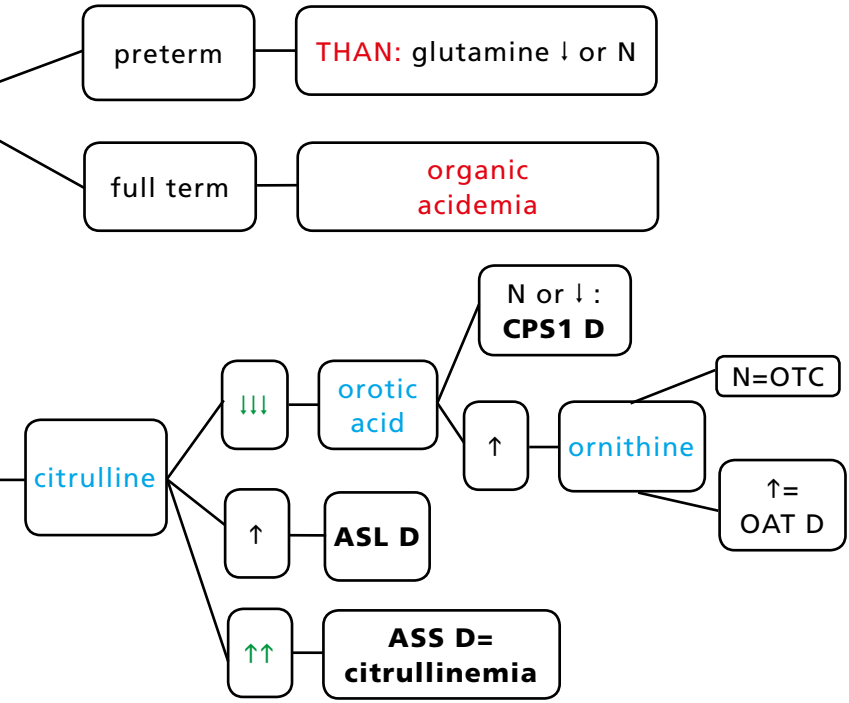



**Fig.3**

*Algorithm for the evaluation of neonatal hyperammonemia, adapted from Burton B. (3) and Häberle et al. (4) (THAN: transient hyperammonemia of the newborn; CPS1D: carbamyl phosphate synthetase deficiency; OTC: ornithine transcarbamylase deficiency; OAT D: ornithine aminotransferase deficiency; ASL D: arginosuccinate lyase deficiency; ASS D: arginosuccinate synthetase deficiency = citrullinemia type 1)*


preterm
THAN: glutamine ↓ or N
full term
organic acidemia
citrulline
↓↓↓
orotic acid
N or ↓ : CPS1 D
↑
ornithine
N=OTC
↑= OAT D
↑
ASL D
↑↑
ASS D= citrullinemia

Table

*Differential diagnosis of neonatal encephalopathy +/- seizures: distinguishing features*

| | Hypoxic-ischemic insult | Intracranial infections / sepsis | Stroke | Intracranial hemorrhage | Extrinsic intoxication | Intrinsic metabolic intoxication |
|---|---|---|---|---|---|---|
| **Medical history** | complicated delivery, abnormal Apgar score | infectious risk may be present (prolonged rupture of membranes, maternal fever pre- or post-partum, Group B streptococcus infection) | complicated delivery common, maternal or placental disorders, cardiac disorders, inherited coagulopathy | preterm, complicated delivery, abnormal Apgar score, neonatal alloimmune thrombocytopenia, inherited coagulopathy | medication given to mother or child | uncomplicated term birth, progressive refusal to feed, vomiting |
| **Symptom-free interval** | no | may be present | variable, occurrence after 24 hours | usually in the first several days of life, rarely present at birth | may occur | may range from 12h to several days |
| **Laboratory** | cord pH, base excess, elevated liver enzymes and decreased renal function, CPK, troponin | abnormal blood count, elevated CRP, PCT and IL6 | no specific laboratory exams but performed to find causes and exclude others diagnosis | complete blood count, baseline coagulation profile | toxicological screening | depending on the disease: abnormal pH, glucose, lactate, ammonia, ketones... |

The differential diagnosis of metabolic causes of neonatal hyperammonemia is obviously not restricted to urea cycle defects, but also includes organic acidemias (propionic aciduria, methylmalonic aciduria), which cause secondary derangement of the urea cycle function, fatty oxidation defects, pyruvate carboxylase deficiency (PCD) as well as several other enzymatic deficiencies (Fig. 3). Organic acidurias are characterized by low blood pH, abnormal anion gab and elevated urinary ketones.

Transient hyperammonemia of the newborn (THAN) should also be considered in premature newborns, keeping in mind that respiratory distress is a prominent early symptom occurring before12 hours of life in THAN, with ammonia levels rising earlier and to higher levels than in UCD (2). THAN is typically characterised by a lack of glutamine elevation.

In our patient, normal pH, absence of organic aciduria, normal acylcarnitines, elevated glutamine and highly elevated citrulline and orotic acid pointed towards the diagnosis of citrullinemia, which was later confirmed by molecular diagnosis. This autosomal recessive urea cycle disorder results from a deficiency of the enzyme arginosuccinate synthetase (ASS), which links citrulline and aspartate to form arginosuccinic acid. ASS1 mutations disabling enzymatic activity lead to severe acute hyperammonemic encephalopathic decompensation within the first days of life, whereas

milder mutations may present after weeks, months or even years with more chronic symptoms (5). In one large published study featuring 70 ASS patients, 34% presented symptoms during the first 30 days of life, 18 % between 1 month and 2 years, 28% between 2 and 12 years, leaving 10% during adolescence and adulthood (6). In the neonatal period, symptoms of hyperammonemia are not very specific: frequently observed findings include poor feeding, vomiting, irritability, tachypnea, somnolence, progressing to lethargy, hypothermia, coma and eventually seizures (7).

Rapid reduction of ammonia is the first goal of treatment in the hyperammonemic neonate, as significant hyperammonemia induces irreversible damage to the developing brain within a few hours. This is achieved by immediately ceasing protein intake, reversing catabolism through high glucose intake, addition of nitrogen-scavenging drugs and hemodialysis if ammonia levels exceed 250-500 µmol/l (8, 9). Detailed recommendations have been published by Haberle et al. (4). In most UCDs, arginine should be added to enhance residual activity of the urea cycle. Addition of N-carbamylglutamate may be considered in undiagnosed UCD patients.

The pathophysiology of hyperammonemia induced brain damage is mediated by complex and not completely elucidated alterations in several amino acid pathways, neurotransmission, failure of energy pro-

duction by the Krebs cycle, impaired creatine metabolism, excessive nitric oxide synthesis, oxidative stress and multiple alterations in signal transduction pathways (7, 10). Glutamine is synthesized in the astrocytes from glutamate and ammonia in an attempt to limit hyperammonemia; this causes astrocytic swelling and thereby cytotoxic edema. Intracellular reversal releases glutamate into the intercellular space. Excessive activation of NMDA receptors by glutamate causes an excitotoxic insult triggering cell death by apoptosis or necrosis (7, 10).

In our patient, initial MRI showed diffuse abnormal signal of the white matter, bilateral globus pallidus lesions, sparing of the thalami, and lesions of the periinsular and perirolandic cortex. Preferential alterations of the white matter and basal ganglia with sparing of the thalami is indeed reported as a characteristic pattern of urea cycle disorders on MRI, helping to differentiate this entity from hypoxic-ischemic lesions (10, 11). In more severe hyperammonemia involving the cortex, the periinsular region is affected first, with progressive extension into the frontal, parietal, temporal and finally occipital lobes (11). Restricted diffusion correlates also with higher and more prolonged ammonia and glutamate levels and more severe neurological sequelae; in the most severe cases, restricted diffusion may even affect the thalami (11).

Overall prognosis of infants with neonatal presentation of UCD is poor with high perinatal mortality. Most surviving patients display moderate to severe mental retardation as well as significant developmental disabilities (4, 10, 12). In a large retrospective study, only 35 % of UCD patients with neonatal presentation survived beyond 11 years, as opposed to 87% of those with later presentation (6). Several authors attempted to correlate the degree of hyperammonemia with clinical outcome: not surprisingly, earlier, higher and more prolonged ammonia levels correlated negatively with neurological outcome (4, 7). Normal psychomotor development is very unlikely when the initial ammonia is >300 µmol/l and when the maximum ammonia reach levels over 480 µmol/l (4). After initial decompensation, long-term outcome is also influenced by external factors, such as the occurrence of infections, stress and poor treatment compliance, which may precipitate further episodes of hyperammonemia causing additional injuries.

Long-term treatment is based on keeping a nutritional balance to avoid malnutrition or catabolism and protein overload that could lead to metabolic decompensation. Dietary protein intake should be kept at the minimum safe level; protein requirements per kg body weight are highest in the neonatal period and decrease steadily as growth slows down. Suggested safe intakes are found in Braissant et al. (7) but must be adjusted individually by regular monitoring of plasma

protein, prealbumin and amino acid levels. In patients with severe UCD, it is often helpful to replace around one fourth of the natural protein by essential amino acids (4). Sufficient calories must be provided, according to age and individual requirements; moreover energy and protein intake should be spread over 24 hours, avoiding long intervals at night that may induce a catabolic state. In addition, the nitrogen-scavenger sodium benzoate or its alternative phenylbutyrate (Ammonaps©) must be given to promote nitrogen excretion (4, 7). These drugs have a narrow therapeutic range; over-dosing may deplete essential amino acids and precipitate catabolism. Arginine becomes an essential amino acid and should be substituted. Daily management is challenging for caregivers and children who live with the fear of a new decompensation that may occasionally require inpatient management in a metabolic center far away from home and ultimately aggravate the child's disability and overall prognosis (12, 13).

Liver transplantation (LT) should be considered an option in particular when there is poor metabolic control. Even if LT prevents further episodes of metabolic decompensation, final outcome obviously depends on the preexisting neurological deficit. Timing of LT requires a balance between the increased risk of performing LT in very small infants and the risk of further episodes of decompensation due to the delay in performing the procedure; some authors advocate therefore transplanting before the age of 1 year (4, 14).

In rare cases when diagnosis is made before birth, sodium benzoate infusion to the mother started a few hours before delivery, along with classical dietary and medical treatment started right after delivery, was shown to prevent neonatal hyperammonemia (5). Neonatal screening for UCDs is not widely promoted as there is no effective sensitive and specific maker and in many cases, severe hyperammonemia occurs before screening results would become available (1, 4).

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