Favorable Long-Term Outcome Following Severe Neonatal Hyperammonemic Coma in a Patient with Argininosuccinate Synthetase Deficiency

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Abstract This chapter reports on the sequelae-free 8-year follow-up with normal growth, intellectual development, and schooling of a boy with argininosuccinate synthetase deficiency (citrullinemia type I) who was rescued from severe neonatal hyperammonemic coma at 8 days of life (peak ammonia level of 1,058 $\mu\text{mol/L}$). Important clinical management aspects were: rapidity of response to emergency therapeutic measures that included specific drug regimen, protein restriction, optimal caloric intake and hemodialysis, short coma duration (14 h), possible neuroprotective effect of mild systemic hypothermia during the acute episode, long-term metabolic control with strict compliance to standard of care therapeutic and dietary regimens, active prevention of subsequent hyperammonemic episodes, and early neurodevelopmental evaluations and interventions. We conclude that good long-term neurological outcome following rescue from neonatal hyperammonemic coma is rarely reported but attainable. Prospective registries and interventional studies regrouping clinical data from urea cycle disorders patients will assist clinicians in instituting the appropriate therapeutic measures to provide the best prospect of positive long-term outcome for these children.

Keywords Argininosuccinate synthetase · Hyperammonemia · Inborn errors of metabolism · Neurodevelopment · Single gene disorder

Abbreviations

ASS Argininosuccinate synthetase
UCD Urea cycle defects

Introduction

Urea cycle defects (UCD) are inherited metabolic disorders leading to abnormal ammonia accumulation. The typical clinical picture associated with severe defects is that of a newborn infant, who, after an uneventful pregnancy and immediate neonatal course, becomes rapidly poorly responsive and evolves toward catastrophic neurological deterioration with seizures, coma, and death. UCD may also present later in life, either as a severe acute episode or as a more chronic course of developmental delay, failure to thrive, and a combination of neurological and digestive manifestations. Treatment options include protein restriction to limit exogenous sources of nitrogen, ammonia clearance through nitrogen-scavenging medications, supplementation with urea cycle intermediates (L-arginine or L-citrulline), and dialysis during acute events. Liver transplantation presents a curative option to achieve long-term metabolic remission (Leonard and McKiernan 2004; Meyburg and Hoffmann 2010).

Access to these treatments has significantly improved the survival of infants with UCD, but the neurological prognosis for survivors of acute hyperammonemic episodes remains uncertain. Children who survive the initial hyperammonemic crisis are at significant risk of disabling neurological sequelae (Msall et al. 1984; Saudubray et al. 1999; Bachmann 2003a; Gropman and Batshaw 2004; Nassogne et al. 2005; Krivitky et al. 2009; Seminara et al. 2010).

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We report on an infant with argininosuccinate synthetase (ASS) deficiency who, despite a catastrophic neonatal presentation of hyperammonemic coma, currently presents adequate cognitive and neurological development over an 8-year follow-up period.

Case Report

This male infant was referred from a distant Northern community hospital at 8 days of life for seizures and coma.

He is the second child of a healthy non-consanguineous French–Canadian couple. Pregnancy was uneventful. Spontaneous vaginal delivery occurred at term. Birth weight was 3.3 kg (25–50th centile), height 52.5 cm (75th centile), and head circumference 34 cm (10–25th centile). APGAR scores were 9, 8, and 8 at 1, 5, and 10 min, respectively. He was a quiet baby who fed well on formula until day 6 of life when, over a 7-h period, he became lethargic and stopped feeding. He was brought to the local emergency department where investigations were undertaken. He was pale and poorly responsive, but the rest of his physical examination was otherwise unremarkable. Vital signs were notable for hypothermia with a rectal body temperature of 34.2°C (N, 34.4–37.8°C). Initial laboratory findings were: blood glucose, 2.4 mmol/L (N, ≥ 2.2 mmol/L and ≤ 7.8 mmol/L); capillary pH, 7.54 (N, 7.37–7.43); pCO₂, 26 torr (N, 26–41 torr); bicarbonate, 21.8 mmol/L (N, 16–24 mmol/L). The following were normal: complete blood count, plasma electrolytes levels, calculated anion gap (10), urinalysis (no ketosis), cerebrospinal fluid glucose and protein levels. A complete septic workup was undertaken, and intravenous hydration with antibiotic therapy initiated pending culture results. Nine hours after admission, focal seizures were noted, which increased in frequency over the next 6 h. The infant was treated with phenobarbital and diazepam and transferred to a secondary care center. At the time of transfer, his vital signs were: pulse 136, respiratory rate 54, blood pressure 102 over 77 mmHg, and rectal body temperature within the lower normal limit at 35.4°C.

Upon arrival at the second hospital, he presented a sustained tonic–clonic seizure and progressively became bradypneic. He was intubated and received additional doses of phenobarbital and phenytoin. Laboratory investigations were repeated with the inclusion of a blood ammonia level, which revealed hyperammonemia at 505 $\mu\text{mol/L}$ (N, <110 $\mu\text{mol/L}$). Other liver function tests were normal. As neither ammonia scavenging medications nor hemodialysis were available at this distant hospital, transfer was immediately arranged to a tertiary care center in a metropolitan area (5-h plane flight). Preparations for immediate drug

treatment and hemodialysis upon arrival at the tertiary care center were made during the time of aerial transport.

The infant was admitted to the intensive care unit with a Glasgow score of 3, severe hypotonia and generalized seizures. Vitals signs recorded on admission were: heart rate 60, blood pressure 82 over 53 mmHg, and rectal body temperature of 33.9°C. Initial ammonia level was 1,058 $\mu\text{mol/L}$. Drug treatment was promptly initiated with intravenous administration over 90 min of a loading dose of 250 mg/kg of each of sodium benzoate, sodium phenylacetate and L-arginine, followed by maintenance continuous infusion of 250 mg/kg/day of each of the previous with the addition of 100 mg/kg/day of L-carnitine. A caloric intake of 130 kcal/kg/day was reached with both intravenous 10% dextrose and 20% intralipid (1 g/kg/day) infusions.

Hemodialysis was instigated 2 h after admission. Ammonia level had by then decreased to 993 $\mu\text{mol/L}$. Body temperature at the time of initiation of dialysis was recorded at 34.0°C and progressive warming with, first, a heating blanket, then a heated bed, was initiated. Within 6 h of combined hemodialysis and drug treatment, blood ammonia level had dropped to 103 $\mu\text{mol/L}$. Glasgow score increased to 6, while body temperature had reached 36.6°C at the end of hemodialysis. Over the next 6 h, Glasgow score progressively improved and seizures stopped. Enteral feeding with protein-free formula (Mead Johnson 80056 Protein Free diet powder) was initiated 12 h after admission to reach an initial enteral caloric intake of 100 kcal/kg/day. Natural proteins were subsequently reintroduced 24 h after admission, at an initial dose of 0.3 g/kg/day.

Blood amino acids chromatography performed upon arrival was notable for elevated glutamine levels at 1,957 $\mu\text{mol/L}$ (N, 474–736 $\mu\text{mol/L}$), citrulline at 3,949 $\mu\text{mol/L}$ (N, 14–32 $\mu\text{mol/L}$), with low ornithine levels of 19 $\mu\text{mol/L}$ (N, 25–103 $\mu\text{mol/L}$), and arginine at 15 $\mu\text{mol/L}$ (N, 43–120 $\mu\text{mol/L}$) (Lepage et al. 1997). Urine orotic acid was measured at 36.53 $\mu\text{mol/mmol}$ of creatinine (N, <3.85 $\mu\text{mol/mmol}$ of creatinine). This biochemical profile was compatible with a diagnosis of citrullinemia type I [MIM 215700, ASS deficiency (EC 6.3.4.5)]. Subsequent sequencing analysis of the ASS1 gene (MIM 603470) revealed an homozygous c.1168G>A (p.G390R) missense mutation (NM_000050.4).

Following full clinical recuperation, the infant was discharged 10 days after admission. His blood ammonia was then 39 $\mu\text{mol/L}$. At discharge, protein intake was restricted at 1.1 g/kg/day, while total caloric intake was maintained at 140 kcal/kg/day. Pharmaceutical treatment at discharge was: sodium benzoate 290 mg/kg/day and L-arginine 250 mg/kg/day both divided four times daily.

He was evaluated monthly for metabolic control and general health until his first birthday. Follow-up appointments

were subsequently gradually spaced, as metabolic control and clinical status were persistently adequate. Pharmaceutical treatment with sodium benzoate and L-arginine was pursued at 250 mg/kg/day each, while protein intake has remained at about 1.0 g/kg/day. Caloric intake was maintained at about 140 kcal/kg/day until 15 months of age, after which it was progressively lowered to reach age-appropriate needs by 2 years of age. He never suffered another hyperammonemic episode and is in general good health. Strict compliance to therapeutic and dietary regimen was observed.

His growth and global development are progressing steadily (weight at the 25th centile, height at the 10th centile, head circumference at the 25th centile). Blood ammonia values have consistently remained below 70 $\mu\text{mol/L}$. Over this 8-year follow-up period, citrulline levels have remained at a median of 1,500 $\mu\text{mol/L}$.

Seizures never recurred and subsequent electroencephalograms were normal. Formal neurological assessments were performed every 2 months during the first year of life, then annually. Slight lower limb hypertonia and abnormal ocular fixation were noted at 2 months of age. Occupational therapy and physiotherapy treatments were promptly initiated. Brain magnetic resonance imaging was performed at 9 months of age and was reported within normal limits, without brain atrophy or other signs of previous brain edema. The only notable finding was an extremely subtle T2-weighted hyper-signal in the white matter of the subinsular cortex. Cortical imaging changes in the insular region have been reported as specific findings in hyperammonemia (Takanashi et al. 2003; Bindu et al. 2009; U-King-Im et al. 2011). Subsequent detailed neuro-ophthalmologic evaluation led to a diagnosis of isolated congenital motor nystagmus, unrelated to a previous neurological insult. Following neurological evaluations did not uncover significant developmental delay over time. No other cerebral imaging was performed.

A complete neuropsychiatric evaluation was undertaken at the age of 4, before school entry. The following intelligence and developmental stage scales were used: WPPSI-III, Leiter-R, and Griffiths. Global intelligence scores (WPPSI-III) and nonverbal intelligence scores (Leiter-R) were both within average. Griffiths developmental stages scores were of 4 years and 5 months for a chronological age of 4 years and 1 month (high average score) for all developmental aspects evaluated (gross motor skills, personal and social, performance) except for language (average, with some vocabulary and fluency difficulties) and for fine motor skills, which were assessed as borderline low to low average. Regular follow-ups in occupational therapy and speech and language therapy were maintained to this day. At 8 years of age, he functions well within a regular schooling system, participates in several out-of-school activities, and is described as an active, curious, and engaging boy.

Discussion

ASS deficiency (MIM 215700) is one of the most prevalent UCD worldwide (Uchino et al. 1998; Summar et al. 2008; Laróvere et al. 2009; Ibarra-González et al. 2010). Complete enzymatic deficiency results in classic or type I citrullinemia (CTLN1), which is typically associated with citrulline elevations above 1,500 $\mu\text{mol/L}$. Most citrullinemia type I patients who suffered their first hyperammonemic episode as neonates are recounted to have died or to face long-term developmental or neurological disabilities (Maestri et al. 1995; Tokatli et al. 1998; Uchino et al. 1998; Bachmann 2003a; Tuchman et al. 2008; Krivitzy et al. 2009; Seminara et al. 2010). Only two cases of ASS-deficient patients are reported with good outcome 2 years following rescue from neonatal hyperammonemic coma (Walter et al. 1992; Vilaseca et al. 2001).

Suggested factors of poor long-term prognosis for survivors of hyperammonemic coma are elevated initial or peak hyperammonemia level and duration and depth of coma (Msall et al. 1984; Bachmann 2003a; Gropman and Batshaw 2004; Tuchman et al. 2008). Msall and colleagues in particular described a significant negative correlation between duration of neonatal hyperammonemic coma (but not with peak ammonia value) and subsequent IQ scores at 12 months. As well, age at onset of symptoms, residual enzymatic activity, compliance to dietary and drug regimen, and subsequent hyperammonemic episodes can each alter long-term outcome (Maestri et al. 1991; Saudubray et al. 1999; Nassogne et al. 2005; Tuchman et al. 2008; Seminara et al. 2010).

Peak ammonia levels for the two neonates described by Vilaseca et al. (2001) and Walter et al. (1992) were of 780 $\mu\text{mol/L}$ and 2,500 $\mu\text{mol/L}$, respectively, but neither level nor duration of coma, dietary, or long-term management measures were precisely stated in those two reports. Although ammonia level at initial presentation is not available, the following is an estimate of our patient's clinical evolution timeline. By the time the child arrived at our center, it had been 31 h since onset of symptoms (lethargy, poor feeding) and 24 h since biochemical signs associated with hyperammonemia were documented (respiratory alkalosis). Clinical coma duration upon arrival at our center was estimated at about 7 h (from onset of tonic-clonic seizures associated with bradypnea). Thus, total duration of hyperammonemia (from onset of symptoms to clinical resolution of both symptoms and hyperammonemia) was estimated at nearly 39 h, while total duration of hyperammonemic coma was estimated at about 14 h. Peak ammonia value was documented at 1,058 $\mu\text{mol/L}$ approximately 8 h after onset of coma. Therefore, our patient fits Msall and colleagues' model, where good outcome is correlated with short coma duration (below 24 h) but not with peak ammonia level.

Survival from hyperammonemic coma has dramatically improved with access to current treatment protocols (Enns et al. 2007). However, intellectual function data from a recent cohort study are sobering: for children aged 3–16 years who presented with neonatal-onset hyperammonemia, half had functional IQ values in the range of intellectual disability, with two-third of those in the moderate to profound disability range, ASS-deficient patients being the most severely affected (Seminara et al. 2010). Moreover, longer follow-ups tend to demonstrate progressive declines in IQ, motor skills deficits, or attention deficits in citrullinemia type I patients rescued from neonatal hyperammonemic coma, even in those who do not suffer subsequent hyperammonemic episodes (Maestri et al. 1995; Krivitzy et al. 2009; Seminara et al. 2010). Although liver transplantation is curative of the metabolic derangement and removes the necessity of strict dietary regimen observance and pharmaceutical treatment for UCD patients, neurologic outcome of these transplanted UCD patients is usually closely correlated to their pretransplantation neurologic status (Whittington et al. 1998; Saudubray et al. 1999; Nassogne et al. 2005; Stevenson et al. 2010). Moreover, hepatic transplantation is a complex surgical procedure with significant risks of peri- and postoperative complications, mortality, and organ rejection. Life-long immunosuppressive therapy is required to maintain engraftment. Living donor grafts from asymptomatic family members is possible, but unrelated donors are few.

Hyperammonemia-induced brain toxicity is thought to occur through several mechanisms: conversion of ammonia to osmotically active glutamine resulting in cerebral edema, increased nitric oxide synthesis and oxidative stress, glutamine-mediated alteration in mitochondrial permeability and metabolism (Cagnon and Braissant 2007; Albrecht et al. 2010; Braissant 2010), and potentially altered neurotransmitter pathways (Enns 2008). Current therapeutic modalities aim to rapidly lower blood ammonia levels and thus reduce its detrimental effects on brain cells. Other currently investigational treatment options to prevent ammonia-induced brain injury include low-grade controlled systemic hypothermia, hypothesized to reduce brain energy demand, both in terms of glucose and oxygen metabolism, restore cerebral blood flow regulation, and decrease intestinal ammonia production (Whitelaw et al. 2001; Chatauret et al. 2002; Stravitz and Larsen 2009).

In our patient, mild hypothermia was neither therapeutically induced nor controlled, but may have played a role both in rapid response to ammonia-lowering therapeutic measures and in neuroprotection. Other factors that had a probable positive impact on our patient's immediate recovery and positive long-term outcome are: rapid institution of hemodialysis, rapid return to enteral feeding once coma had resolved, optimal caloric intake both during the acute episode and during long-term management, strict compliance to

pharmaceutical and dietary regimen, and active prevention of subsequent hyperammonemic episodes.

Genotype–phenotype correlations as an aid to clinical management of ASS-deficient patients have been attempted. Wide phenotypic variability has been reported among individuals with ASS deficiency, even among members of the same family (Issa et al. 1988). The c.1168G>A (p.G390R) missense ASS1 variant identified in our patient is so far the single most common variant identified in early-onset citrullinemia type I (Kobayashi et al. 1990; Häberle et al. 2002; Gao et al. 2003; Engel et al. 2009; Laróvere et al. 2009). Homozygosity for this variant is usually associated with undetectable or severely reduced (less than 2%) residual enzymatic activity (Kobayashi et al. 1990; Vilaseca et al. 2001; Gao et al. 2003; Berning et al. 2008). Although associated with severe enzymatic deficiency and neonatal-onset hyperammonemia, this genotype does not systematically equate with poor long-term outcome, as demonstrated in our patient.

Newborn screening aims in part at instituting rapid therapeutic interventions for infants at risk of life-threatening disorders. Citrullinemia neonatal screening permits early treatment of newborns at risk and likely affects both survival and cognitive outcome. One caveat of citrullinemia newborn screening is that most patients with severe, early-onset forms usually present clinically before screening results are available (Bachmann 2003b; Wilcken et al. 2009). Moreover, newborn screening programs worldwide have now identified individuals with elevated citrullinemia ($>3,000 \mu\text{mol/L}$) who remain asymptomatic (Wilcken et al. 2009; Wilcken 2010). Debate on how these patients should be managed is still ongoing, although recent reports of asymptomatic adult citrullinemia patients experiencing their first hyperammonemic episode during pregnancy or the postpartum period do argue in favor of protein restriction even for “mild” cases.

Thus, several inherited and environmental factors play important roles in the initial presentation, therapeutic response, and long-term evolution of patients with ASS deficiency. Reliable clinical indicators of disease course and severity are currently lacking. There are inherent difficulties in comparing and interpreting the data of survivors of neonatal hyperammonemic episodes published over the past 20 years: lack of uniform initial clinical management across medical centers and lack of systematic documentation of clinical elements that could potentially modify treatment response or long-term evolution. Detailed prospective clinical registries as well as longitudinal interventional studies are essential to resolve this important issue, as an event-free course and optimal long-term quality of life are the goal to reach for these patients. The Urea Cycle Disorders Consortium, a network of 15 clinical and research centers providing care for UCD patients, has established a national research and clinical registry in the USA with collaborators in Canada

and in Switzerland that will help in providing comprehensive data to improve clinical management and outcome for UCD patients.

Conclusion

Although the prognosis of neonatal hyperammonemic coma is traditionally considered as guarded, both in terms of survival and long-term neurological outcome, our case shows that recuperation from a severe neonatal hyperammonemic episode without long-term impairment is possible. The following factors were likely influential in the favorable evolution of our patient: rapid therapeutic intervention with appropriate ammonia-lowering measures and optimal caloric intake to reverse catabolism, fast lowering of blood ammonia during the acute episode, short hyperammonemic coma duration, strict long-term metabolic control with optimal compliance to pharmaceutical and dietary regimen, as well as aggressive prevention of subsequent hyperammonemic episodes. Registries and prospective studies in neonates treated with the current standardized clinical protocols will prove invaluable in assessing the precise impact of each of these elements in the long-term management of these high-risk patients.

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Synopsis

We describe the favorable long-term neurological outcome of a boy with argininosuccinate synthetase deficiency who presented with severe neonatal hyperammonemic coma.

References to Electronic Databases

Argininosuccinate synthetase 1; citrullinemia, classic: MIM 603470; 215700

Argininosuccinate synthetase: EC 6.3.4.5

ASS1 gene: geneID 445; NM_000050.4

Competing Interest Statement

Each author declares that the answer to all questions on the JIMD Reports competing interest form are “No,” and therefore they have nothing to declare.

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