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RESEARCH REPORT

Normal Neurological Development During Infancy Despite Massive Hyperammonemia in Early Treated NAGS Deficiency

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Abstract A girl born at term was admitted to the neonatal intensive care unit because of mild respiratory distress after a complicated delivery. She recovered, but was readmitted at 58 h of life with mild respiratory distress and increased muscle tone. Neonatal abstinence syndrome because of maternal use of lithium, clomipramine, and quetiapine during pregnancy was suspected, but at 115 h of life she became unresponsive, and an immediate work-up for coma was initiated. An ammonia of 2,235 μmol/l was found, and treatment with sodium benzoate, sodium phenylacetate, arginine, glucose, and *N*-carbamylglutamate (NCG, Carbaglu®) was started. This treatment normalized plasma ammonia levels within 16 h.

Biochemical results suggested a mitochondrial urea cycle defect, either of *N*-acetyl glutamate synthase (NAGS) or carbamoyl phosphate synthetase 1. DNA analysis later confirmed a diagnosis of NAGS deficiency. Under long-term treatment with NCG, the patient developed normally at last follow-up at 7 months of age.

In conclusion, the standard neonatal situation of a neurologically compromised newborn turned out as a treatable rare inborn error of metabolism. In all neonates with somnolence and coma and hence the suspicion of a bacterial sepsis, plasma ammonia should be included in the work-up. NCG was immediately beneficial for the patient described and should be considered for the emergency treatment of neonatal hyperammonemia. Even a very high ammonia may allow for a normal neurological development in infancy (and possibly beyond).

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Case Report

Our patient, a baby girl, is the first child of unrelated, healthy parents. In pregnancy the mother was treated with clomipramine, lithium, and quetiapine due to bipolar disease. She was born 2 days before estimated day of delivery, 64 h after rupture of membranes. A vacuum extraction was performed because of suspected intrauterine hypoxia. She had Apgar scores of 6, 7, and 8 after 1, 5, and 10 min, respectively, and a birth weight of 3,380 g.

Shortly after birth she was admitted to the neonatal intensive care unit because of mild respiratory distress and was treated with nasal continuous positive airway pressure (CPAP) and antibiotics, and recovered in a few hours. She was fed formula by bottle.

Apart from a blood glucose of 1.1 mmol/l (normal $\geq$2.2 mmol/l) 6 h after birth, blood count, electrolytes, ionized calcium, and capillary acid base were normal. CRP was a maximum of 20 mg/l (normal <5 mg/l). Blood cultures remained negative.

She was discharged to the maternity unit at 48 h postnatal age but readmitted 10 h later with mild respiratory distress and general increased muscular tone. Blood pressure was 112/78 mmHg, capillary pCO_2 5.0 kPa with

a pH of 7.44. Neonatal abstinence syndrome due to maternal quetiapine use was suspected, and treatment was started with phenobarbital. Formula was given by nasogastric tube.

From 88 h of age she had apneic episodes, and after failure of nasal CPAP she was intubated at 100 h of postnatal age because of respiratory failure, after analgesia with fentanyl 3 μg/kg. At 115 h of age she did not respond to pain or suction, and had no spontaneous ventilation. Therefore, a work-up for neonatal coma was immediately started. Ultrasound of brain was normal, CRP was negative, but arterial ammonia was highly elevated (2,235 μmol/l, normal <100 μmol/l). Buffer base was 2.1 mmol/l (normal −3.0 to +3.0), alanine aminotransferase 21 U/l (normal 7–40), quetiapine was undetectable, lithium 0.3 mmol/l (therapeutic range for adults 0.5–1 mmol/l).

With ammonia levels above 400–500 μmol/l, invasive extracorporeal detoxification is recommended (Häberle et al. 2012). Since the prognosis in the presence of severe hyperammonemia was considered grim, it was decided, after discussion with the parents, to limit treatment to a trial of sodium benzoate, sodium phenylacetate, L-arginine, and NCG.

On start of this emergency treatment for hyperammonemia (at 120 h of age), ammonia was further increased to 2,455 μmol/l, but 3 h later already declined to 1,746 μmol/l, and 16 h after treatment was started ammonia was in the normal range (36 μmol/l).

With normalized ammonia the patient became awake again but was extremely irritable. She also had abdominal distension and bloody diarrhea, and on day 7 required laparotomy for a partial gangrenous large bowel resection and enterostomy.

Plasma for analysis of amino acids was taken approximately 30 min after start of loading dose of sodium benzoate, sodium phenylacetate, and L-arginine, which was likely the cause for the elevation of arginine (938 μmol/l, normal 17–120), while glutamine was only slightly elevated to 872 μmol/l (normal 400–850), and citrulline was unmeasurably low. In urine, excretion of orotic acid was normal. Analysis of urine and plasma did not show evidence of an organic aciduria or a fatty acid oxidation defect. Biochemical results therefore suggested a urea cycle defect, either of *N*-acetyl glutamate synthase (NAGS) or of carbamoyl phosphate synthetase 1 (CPS1).

Given the fast response to the above treatment NAGS deficiency was suspected. This was later confirmed by DNA-analysis, which identified a known homozygous nonsense mutation in exon 4 of the *NAGS* gene, c.971G>A (p.Trp324*) (University Children's Hospital, Zürich, Switzerland) (Sancho-Vaello et al. 2016). The parents were confirmed to be heterozygous for the same mutation.

After gradual decrease of the above medical treatment, the patient was discharged at 5 weeks of age. By that time she was feeding well, on treatment with NCG 40 mg/kg/day, without any dietary restriction or other medication. She smiled at 7 weeks. At 7 months she develops normally. Her enterostomy has been closed without any complications. Plasma ammonia levels on follow-up remained normal.

Discussion

Hyperammonemia

Elevated ammonia is a major problem and the main cause of disease in urea cycle defects (Gropman et al. 2007; Msall et al. 1984). Ammonia may also be elevated in organic acidemias, fatty acid oxidation disorders, and in other inherited and a few acquired conditions (Häberle 2013). Ammonia is extremely toxic for the central nervous system (Braissant et al. 2013), and levels above 360 μmol/l are associated with a poor prognosis, either death or severe developmental delay (Kido et al. 2012). Prognosis is considered very poor with ammonia levels above 1,000 μmol/l, although the impact of the absolute value also depends on the duration of hyperammonemia (Häberle et al. 2012; Picca et al. 2001). With timely treatment several patients with NAGS deficiency have had a normal outcome (Sancho-Vaello et al. 2016).

Standard treatment for moderate hyperammonemia without known diagnosis has been sodium benzoate, sodium phenylbutyrate or sodium phenylacetate, and L-arginine, and recent guidelines suggest NCG to be added to the initial treatment (Häberle et al. 2012). Hemofiltration or hemodialysis is recommended with ammonia levels above 400–500 μmol/l, but this threshold is rather based on empirical and circumstantial evidence than on proper studies. In many patients it will take several hours to establish the vascular access to start dialysis, and there is a risk of complications with this technique.

N-Acetyl Glutamate Synthase (NAGS) Deficiency

NAGS deficiency is probably the rarest urea cycle disorder, with just over 50 published cases worldwide (Sancho-Vaello et al. 2016). Diagnosis is best achieved by genetic

analysis (Häberle et al. 2012). As this diagnosis is not obvious from ordinary metabolic screening, cases may remain undiagnosed. It is the only disorder within the urea cycle which can be specifically and effectively treated by a drug, with no dietary restriction outside catabolic circumstances (Gessler et al. 2010; van Leynseele et al. 2013).

Clinical Significance

- Any somnolence or coma in the neonate, especially following a short symptom-free interval after birth, should be investigated for hyperammonemia, even without hyperventilation with corresponding low pCO_2 and elevated pH.
- *N*-carbamylglutamate should be added to the standard protocol for treatment of hyperammonemia, together with sodium benzoate, sodium phenylbutyrate, and L-arginine.
- Response to *N*-carbamylglutamate in NAGS deficiency may be so rapid that dialysis may be omitted.
- Even with very high ammonia levels later development may be good in cases in which hyperammonemia lasts for only a few hours.

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Compliance with Ethics Guidelines

Conflict of Interest

Hallvard Reigstad and Berit Woldseth declare no conflict of interest. Johannes Häberle has received travel support and honoraria as an invited speaker from Orphan Europe Recordati.

Informed Consent

Informed consent was obtained from the parents of the patient.

This chapter does not contain any studies with human or animal subjects performed by any of the authors.

Hallvard Reigstad has been responsible for the treatment and follow-up of the patient, and is the main author of this chapter.

Berit Woldseth has been responsible for the biochemical analyses and has revised the chapter.

Johannes Häberle has been responsible for the genetic analyses and has revised the chapter.

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