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Irritability, Poor Nutrition, and Respiratory Alkalosis in Neonates: Brief Summary of Hyperammonia Management

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Abstract: **The urea cycle is a series of metabolic reactions that convert ammonia into urea to remove it from the body. Urea cycle disorders are characterized by hyperammonemia, which can cause irreversible damage to the central nervous system. We report a series of three infants presenting with irritability, poor feeding, and rapid breathing. Their first gas analysis revealed respiratory alkalosis. Hyperammonemia was confirmed and three different urea cycle enzyme blocks were diagnosed. Immediate treatments for include removal of ammonia by reducing catabolism, dietary modification, use of nitrogen scavengers, and finally dialysis. Hyperammonemia is a medical emergency that should not delay treatment. This report aims to emphasize the importance of suspecting a urea cycle disorder in neonates with nonspecific signs of hyperammonemia and respiratory alkalosis, and to summarize the main management directions for hyperammonemia.**

Keywords: **hyperammonemia; respiratory alkalosis; urea cycle disorder; newborn; continuous venovenous hemodia filtration.**

I. INTRODUCTION

Any total or partial enzyme deficiency or transport defect in this pathway leads to a urea cycle disorder (UCD), resulting in acute hyperammonemia except for the arginase deficiency [3]. The initial symptoms of hyperammonemia are hyperventilation with irritability evolving to coma [1]. Hyperventilation in UCDs is a common early finding which causes respiratory alkalosis. Increasing cerebral edema may result in progressive encephalopathy with hypoventilation and respiratory arrest. Urea cycle disorders have autosomal recessive inheritance pattern except for ornithine transcarbamylase (OTC) deficiency, which is X-linked [6]. The initial presentation can occur at any age; approximately half of all patients are newborns developing symptoms within the first 12 to 48 h after birth. The diagnosis of UCD can be made either on clinical basis or by neonatal screening in some countries. Newborn screening allows an early diagnosis and intervention even before symptoms appear. Screening programs are essentially based on the Wilson and Jungner criteria [9] and target

illnesses with important health issue whose early diagnosis and treatment can lead to a direct improvement in the patient's quality of life. However, variations in the criteria for neonatal screening have emerged as a result of technological progress (molecular biology, mass spectrometry), medical advances and even public demand. Thus, the list of diseases that can now be detected in the neonatal period is becoming technically very important and should be constantly updated. In Belgium, both the Dutch speaking and the French speaking communities use the Guthrie test for their neonatal screening programs. The list of the diseases to screen is decided by each community, according to their own legal criteria.

II. CASE REPORTS

The three reported patients were admitted to neonatal or pediatric intensive care units betweenApril and October 2017.

Their gestational ages ranged from 36 to 41 weeks. Pregnancy was properly monitored and uneventful for all of them. Birth weights were normal for gestational age, except for case 3 who was dysmature (Table 1). No consanguinity was reported among the parents of the three patients. They did not require any cardiopulmonary resuscitation in delivery room. They were admitted to the neonatal or pediatric intensive care units between the first and the seventh day of life owing to similar symptomsas poor feeding, lethargy, irritability and sleepiness. Respiratory distress and hyperventilation were remarkable as well (Table 1).

Table 1. Personal information, symptoms, diagnostic laboratory data and diagnosis of the cases.

	Case 1	Case 2	Case 3
Gestational age (weeks)	41 + 1/7	39	36
Birth weight (grams)	3260	3830	2035
Gender	Boy	Boy	Girl
Admission to intensive care unit (days of life)	2	1	7
Symptoms at admission	Sleepiness; Hypotonia Irritability; Tachypnea	Irritability and poor feeding	Sleepiness; Lethargy; Irritability; Tachypnea
Initial blood gas analysis (capillary)	Respiratory alkalosis (pH 7.60; pCO2 22.3 mmHg; HCO3 21.5 mmol/L)	Respiratory alkalosis (pH 7.52; pCO2 24 mmHg; HCO3 19.5 mmol/L)	Respiratory alkalosis (pH 7.55; pCO2 26 mmHg; HCO3 22 mmol/L)
Initial ammonia plasma level (µmol/L)	775	527	845
Blood amino acids	Low plasma levels of citrulline, argininosuccinic acid and arginine; High plasma level of glutamine	Low plasma levels of citrulline and arginine; High plasma level of glutamine	High plasma level of citrulline; High plasma level of glutamine
Urinary orotic acid	High	Normal	High
Diagnosi	Ornithine transcarbamylase (OTC) deficiency	Carbamoyl-phosphate synthetase (CPS) deficiency	Argininosuccinic acid synthetase (ASS) deficiency
Genetic analysis	Mutation in c996G > A (p.Trp332) of the OTC gene ina haemizygote state	Missense mutation c.4142C > T (pLeu1381Ser) in exon 35 of the CPS 1 gene in a heterozygous state	Mutation in variants c.773 + 49C >T and c.1168G > A (pGly390Arg) of the ASS1 gene in a heterozygous state
Length of stay in intensive care unit	28	24	8

Initial plasma ammonia levels were high between 527 and 788 µmol/L (normal range: 48–110 µmol/L) (Table 1). The immediate first therapeutic line for all patients consisted in invasive ventilation support because of neurologic impairment, glucose infusion (10 mg/kg/min) after stopping protein intake, administration of ammonia scavengers (intravenous sodium benzoate) and arginine. Protein-free therapy was instituted rapidly to prevent a rebound of plasma ammonia levels. As since enteral feeding was tolerated (between two and eight days after admission to intensive care units), the patients received a low-protein diet adapted to plasma ammonia levels and plasma amino acids. Despite first-line therapy, hyperammonemia persisted in each case and blood gases progressed to acidosis for the two boys. Therefore, continuous venovenous hemodiafiltration (CVVHDF) was rapidly initiated for all of them, thus permitting a significant decrease in plasma ammonia

levels (Figure 1). Biochemical investigations including hepatic enzymes, glycemia, lactatemia, plasma amino acids, urinary orotic acid, urinary ketone bodies and urinary organic acids were performed to find the enzyme deficiency. Carglumic acid, generally used for the treatment of hyperammonemia in patients with N-acetylglutamate synthase deficiency [1,11] was started empirically along with the first therapeutic line. Due to its inefficiency in the management of hyperammonemia in our patients, and after receiving the results of the first biological tests (12 to nearly 48 h after starting dialysis), which excluded a deficiency in N-acetylglutamate synthase, this treatment was, therefore, stopped (Figure 1). Electrophysiological, as well as neurologic signs improved in all patients, thus correlating with the ammonia plasma level drop.

Genetic analysis confirmed all three diagnoses. Various methods were used, including parallel mass sequencing (on a panel of 3989 genes involved in metabolic diseases). Mutations found in the ASS 1, CPS 1, and OTC 1 genes confirm the three diagnoses (Table 1). These variants, which have been described, are associated with the observed phenotypes. A genetic analysis was also requested from the parents of our patient: the mother of case 1 was proven to be a carrier of the mutation; for cases 2, both parents are mutation carriers; Unfortunately, the parents of case 3 were unable to perform genetic analysis. Their discharge treatments were the same: a low-protein, high-energy diet, sodium benzoate, L-citrulline, and arginine. At 14 months of age, Case 3's psychomotor development was normal. His movements are smooth and well coordinated. Case 2 had mild axial hypotension at the same age; despite this, his movements are fluid and well-coordinated. However, he needs Bobath's support in physical therapy.Their growth parameters were within the normal range for age. Unlike the others, case 1 had more severe neurological sequelae with gross growth retardation, axial hypotension, and persistent convulsions. Due to poor quality of life, dietary restrictions with recurrent metabolic decompensation and hospitalization, cases 1 and 2 received liver transplantation at 10 and 16 months, respectively.

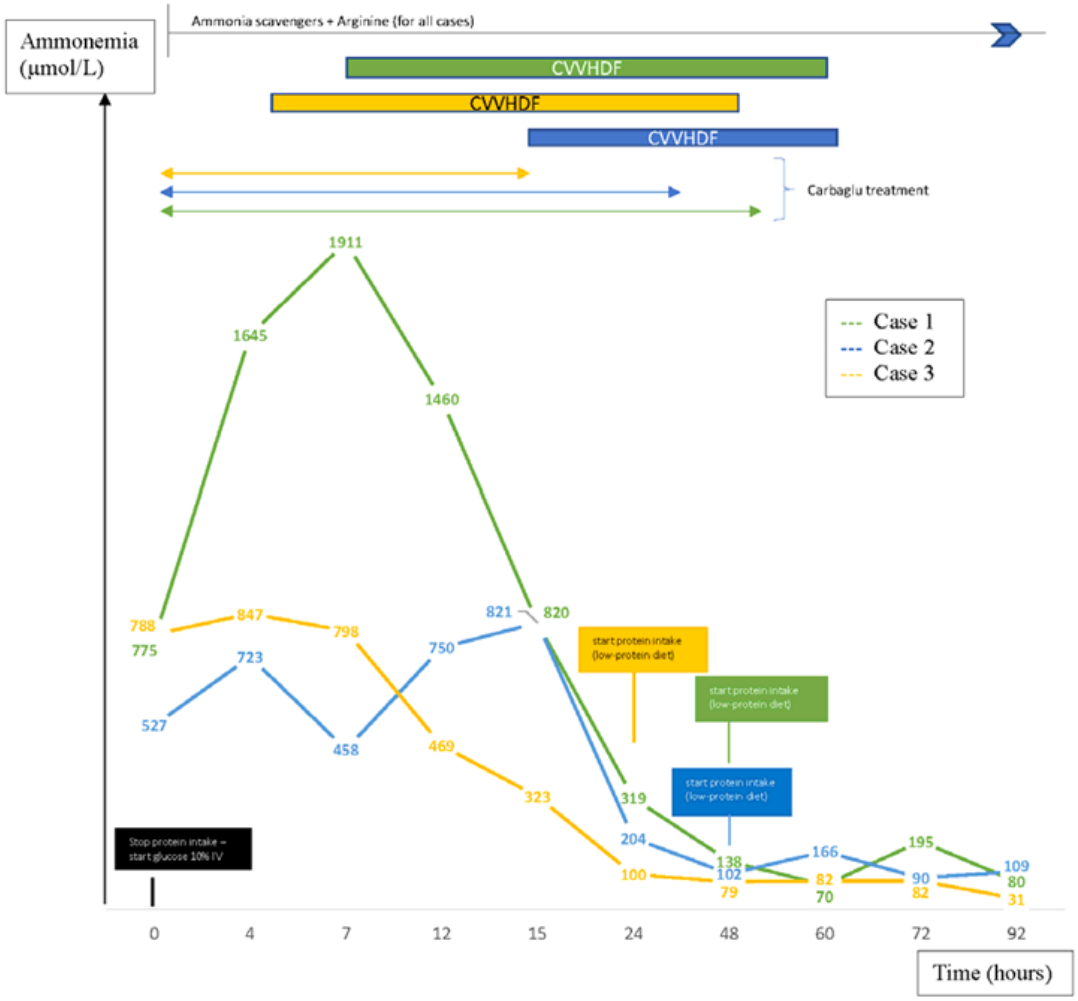

Figure 1. Evolution of ammonemia.

III. DISCUSSION

This report aims to highlight the importance of non-specific signs and especially respiratory alkalosis in newborns as a clue of suspicion for urea cycle disorders. As hyperammonemic crisis could cause severe neurologic sequelae, this should be considered as a medical emergency and first-line treatment should not be delayed. Therefore, starting from the description of three cases, another purpose of this work is to take a look at the acute management of hyperammonemia in newborns. As noted in two of our cases, respiratory alkalosis can progress to acidosis, mostly if UCDs are diagnosed and treated late [1,5]. Respiratory alkalosis (high serum bicarbonate and high arterial pH) with normal anion gap and blood glucose in a newborn should prompt immediate plasma ammonia measurement, as hyperammonemia is initially present in 50% of acute urea cycle disorders [1]. Hyperammonemia is defined as a plasma ammonia level greater than 110 µmol/L for neonates born at term. However, hyperammonemia is present in UCDs mostly at higher values (>200 µmol/L) [4]. If the ammonia plasma value is between 110 and 200 µmol/L, a control is recommended. An idiopathic disorder known as transient hyperammonemia of the newborn (THAN) can occasionally be present in preterm newborns as well, characterized by a normal blood glutamine level and not always symptomatic [1]. If plasma ammonia is elevated, further basic laboratory and metabolic investigations (determination of plasma amino acids, plasma acylcarnitines, urinary organic acids and orotic acid) might be immediately carried out without delaying specific treatment [1].Hyperammonemia in neonates is either primary, due to an enzymatic block in the urea cycle, or secondary, due to organic acid disorders, fatty acid oxidation defects, congenital sepsis or severe hepatic insufficiency [13]. The plasma level of glutamine and urea cycle intermediates (citrulline and arginine) are helpful to distinguish between primary and secondary hyperammonemia [1]. Urea cycle disorders were suspected rapidly because of the respiratory alkalosis, the presence of elevated plasma glutamine level and disturbed plasma values of urea cycle intermediates. Our cases manifested typical severe neonatal forms of urea cycle disorders as they presented, in the very first days of life severe hyperammonemia, encephalopathy and seizures. Moreover, ammonia scavengers are the main drugs useful to bypass the urea cycle, thus contributing to reduce plasma ammonia level. However, both are effective choices, and are recommended when plasma ammonia levels are between 150 and 250 µmol/L. Although carnitine is still part of this acute treatment in Europe (particularly in Spain), our patients did not receive this molecule because it has been proven to have little benefits in UCDs and it is, therefore, not recommended anymore by the latest European guidelines [1,14]. Continuous venovenous hemodiafiltration (CVVHDF) should be initiated urgently in patients unresponsive to dietary and pharmacological treatments, perhaps systematically when plasma ammonia levels rise above 500 µmol/L [1]. Despite the first therapeutic line, increased plasma ammonia levels were still observed in all our patients, which led us to start CVVHDF. As soon as severe hyperammonemia is detected, the patient should be immediately transferred to a center where hemodiafiltration is available. Dietary treatment for UCDs varies significantly among European Inherited Metabolic Diseases centers. In these patients, it has been recommended to administer the 20–30% (up to 50% in ARG1 deficiency) of the entire protein intake as EAA in order to maintain growth and metabolic control [1]. including 464 patients with UCDs from several European countries, only 30% of the cases in United Kingdom received this EAA supplementation and in the rest of the Europe these rates average 38%, with notable differences among countries (100% in Sweden, 67% in Portugal, 64% in Germany, 38% in Belgium, 29% in Italy and 24% in France) [15]. EAA are rather recommended for patients with UCDs [16]. Seizures are present in almost 50% of neonates diagnosed with hyperammonemia [17] and were observed in all our newborns. Neurologic outcome is very poor in presence of intracranial hypertension and/or if plasma ammonia peaked at above 1000 µmol/L, although the impact of this level on prognosis depends on the duration of hyperammonemia [1]. The case 1 reached the highest plasma levels with a peak above 1000 µmol/L during almost 12 h and developed later serious psychomotor development issues. Damages in central nervous system are reported to be irreversible when peak plasma ammonia levels rise above 480 µmol/L already [1,5]. Nevertheless, case 3 had a normal psychomotor development at 14 months of age even though she had the highest initial plasma ammonia level at diagnosis, but of short duration and with rapid improvement (normalization of ammonemia 12 h after starting treatment). Italy is the European country where the highest number of inborn errors of metabolism (IEM) are tested in neonatal screening programs (including, among others, type 1 and type 2 citrullinemia, argininosuccinic aciduria and hyperargininemia for the UCDs).However, some European countries (such as France, Germany, Austria, Switzerland or Denmark) consider that most pathologies affecting the urea cycle are not eligible for inclusion in the group of diseases to be screened at birth for several reasons: high number of false positives, lack of consensus on the individual benefits of early intervention, low number of patients described in the literature, early onset of symptoms before results of test are known and lack of evidence on the effectiveness of screening [20].

IV. CONCLUSIONS

Timely diagnosis of hyperammonemia requires a high index of suspicion. Plasma ammonia should be measured in all newborns with unexplained symptoms such as poor feeding, irritability, lethargy,particularly in presence of tachypnea. The presence of respiratory alkalosis is an early sign that will guide the diagnosis for urea cycle disorders. As delay in treatment may result in progressive neurologic injury, or even death, a correct diagnosis should be established as soon as possible. The appropriate conservatory management is critical. The access to the CVVHDF should be anticipated and granted ifunsatisfactory response to first-line therapy.

As UCDs represent an important health problem because of irreversible sequelae if misdiagnosed and untreated, a single rapid and valid method of screening to help diagnosis might be desirable allover Europe.

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