Challenges in the diagnosis and management of urea cycle disorders in Romanian children

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Abstract

Pediatricians should be aware of the clinical presentation, emergency intervention, and long-term management of hyperammonemia. In Romania, there are many challenges regarding hyperammonemia: low awareness of the need for prompt diagnosis and adequate management, communication problems between different physicians, lack of knowledge and availability of diagnostic tools and medications, lack of dietitians trained in metabolic diseases.

Urea cycle disorders (UCD) are severe diseases, with high mortality in neonates and possible neurologic complications in the survivors. Clinical presentation is variable, with the onset at any age. It is crucial for a correct and early diagnosis that the first physician sees a patient with symptoms of hyperammonemia to think of it. Pediatricians should suspect UCD in neonates or children with hyperammonemia without metabolic acidosis and hypoglycemia. Neonatal sepsis is the most frequent misdiagnosis. Pediatricians and parents of a child with UCD should be aware of the potential triggers of hyperammonemia. Emergency treatment to reduce the ammonia level should be initiated as quickly as possible. Long-term treatment aims to obtain metabolic control and achieve normal development and growth. A multidisciplinary approach in managing these children improves survival chances and the long-term quality of life.

Keywords: hyperammonemia, urea cycle disorders, diagnosis, treatment, children

Hyperammonemia is a life-threatening condition with possible severe neurologic consequences. Pediatricians should be aware of the clinical presentation, emergency intervention, and long-term management of these patients to improve patients' quality of life. The most frequent causes could be liver failure, an inborn error of metabolism (IEM), or exposure to toxics and medication [1].

In Romania, there are many challenges for medical professionals and patients regarding hyperammonemia: low awareness of the need for prompt diagnosis and adequate management, communication problems between different physicians, lack of knowledge and availability of diagnostic tools and medications.

The normal value for ammonia level varies with the age of the patient. Hyperammonemia is defined as a plasmatic level above 150 µmol/L in premature neonates, above 100 µmol/L in term neonates, above 40 µmol/L in infants and children, and above 32 µmol/L in adults [2].

The urea cycle is the main pathway for the elimination of excess nitrogen [3]. Hyperammonemia is associated with neurological manifestations, from lethargy to coma, anorexia, vomiting, hyperventilation, and hypothermia. Prevention of the toxicity of ammonia should be the primary goal of treating hyperammonemia [2].

Urea cycle disorders (UCD) are severe diseases that can result in acute or chronic hyperammonemia and cause it in 23% of the patients [1]. Half of the neonatal period cases with hyperammonemia are

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with high mortality and neurologic complications in the survivors [4].

Ornithine transcarbamylase (OTC) deficiency, an X-linked disorder, is the most frequent UCD with a prevalence of 1/14,000 to 1/77,000 live births. In males, OTC is usually lethal in the neonatal period but also can have milder forms. In females, OTC clinical presentation is variable, up to 20% being with a severe presentation. In the other cases being with subtle symptoms or with spontaneous resolution of the acute episodes without intervention [1,4].

All the other UCD are autosomal-recessive disorders and are due to defects of the urea cycle enzymes or transporters: N-acetyl glutamate synthetase (NAGS) deficiency, carbamoyl phosphate synthetase 1 (CPS1) deficiency, argininosuccinate synthetase (ASS) deficiency, argininosuccinate lyase (ASL) deficiency, arginase 1 deficiency (ARG1D), citrullinemia type 2 and hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome [1,5].

Clinical presentation of UCD is variable, with the onset at any age, but more common during periods with metabolic stress: neonatal period, late infancy, and puberty. As the early symptoms are non-specific, diagnosis may be easily overlooked. It is crucial for a correct and early diagnosis that the first physician sees a patient with symptoms of hyperammonemia to think of it and suspect UCD [3].

Clinical manifestations of neonates have the onset shortly after the birth (even less than 24 hours, early-onset UCD): poor feeding, vomiting, lethargy progressing to somnolence or coma, irritability, tachypnea, hypothermia. In infancy, after 28 days of life (late-onset UCD), the presentation is less severe and more variable with anorexia, lethargy, vomiting, failure to thrive, insufficient developmental progress, behavioral problems, hepatomegaly, and non-specific gastrointestinal symptoms. Children and adolescents present with neurological manifestations, confusion, irritability, episodic vomiting. Usually, their symptoms follow metabolic stress precipitated by different factors. Between acute episodes, there are no clinical manifestations, and the children are relatively well. There could also be some learning difficulties or even mental retardation [3,6].

In all suspected patients with UCD, it is essential to take a careful medical history, including drug intake, family history of unexplained neonatal death, neurological disease, or protein aversion [4].

Pediatricians and parents of a child with UCD should be aware of the **potential triggers of hyperammonemia**:

- Infections (mainly gastroenteritis), fever, vomiting,
- Bleeding (gastrointestinal or internal),
- Decrease intake of proteins or energy (fasting, significant weight loss in neonates),
- Chemotherapy, high-dose glucocorticoids, drugs (valproate, l-asparaginase/pegaspargase, but also topiramate, carbamazepine, phenobarbitone, phenytoin, furosemide, hydrochlorothiazide, salicylates),
- Prolonged or intense physical exercise, surgery under general anesthesia,
- Unusual protein loads (barbecue, parenteral nutrition, protein supplements) [2,4].

Plasma ammonia level should be measured in any sepsis workup in a neonate without an apparent infection, in any child of any age with an unexplained changed in consciousness, neurological manifestations, liver failure, or suspected intoxication [2,4,7]. Respiratory alkalosis in a newborn should prompt immediate measurement of ammonia level as is characteristic for UCD [4].

Blood, and not serum, is recommended for ammonia determination, and it should be collected in a prechilled tube without using a tourniquet and transported on ice immediately to the laboratory. Plasma should be separated within 15 minutes from the collection as ammonia is stable for under 15 minutes at 4°C [1]. Arterial or venous blood can be used, but not capillary blood [7]. We use at bedside another method for ammonia determination, dry chemistry based on a micro diffusion method with whole blood to measure the intensity of the color after reaction with bromocresol green. This point-of-care measurement can be done at room temperature in 3 minutes, but this method's limit is the cut-off range of 8-285 µmol/l [1]. False-positive results are due to the hemolysis or delay in processing the sample for a long time at room temperature will increase the ammonia level [1,7].

Initial diagnosis workup in a patient with hyperammonemia: repeat plasma ammonia, venous/arterial blood pH and gases, plasma chemistry (glucose, electrolytes, anion gap, blood urea nitrogen, creatinine, lactate), liver function tests (transaminases, bilirubin, albumin, alkaline phosphatase) and clotting studies, blood culture, complete blood count, plasma amino acids, urine ketones, urine organic acids and urinary orotic acid, acylcarnitine profile, total, free carnitine [3,8].

Pediatricians should suspect UCD in neonates or children with hyperammonemia without metabolic acidosis and hypoglycemia [2]. Neonatal sepsis is the most frequent misdiagnosis in the early presentation of UCD [4]. Samples for plasma amino acids and urinary amino acids, organic acids, and orotic acid should be taken before any treatment, without delaying the transport and intervention [7]. The guidelines for diagnosing and managing UCD mention that most of the patients did not present liver diseases. Diagnosis may be guided by the level of amino acids in plasma or urine: urinary orotic acids with low plasma level of citrulline and arginine (OTC), elevated level or arginine and argininosuccinic acids (ARG and ASL deficiencies), hypercitrullinemia without an increase of argininosuccinic acid (ASS deficiency), low or normal urinary orotic acid and low plasma level of citrulline and arginine (CPS or

NAGS deficiency), or high blood ornithine and urinary homocitrulline (HHH syndrome) [2].

Other possible causes of hyperammonemia are organic acidurias (methylmalonic aciduria, MMA, propionic acidemia, PA, isovaleric acidemia, IA). In these conditions, hyperammonemia is associated with severe metabolic acidosis with a high anion gap and ketonuria. Fatty acid oxidations defects may present with associated hypoglycemia, high creatin-kinase, and cardiomyopathy. HMG-CoA lyase deficiency, pyruvate carboxylase deficiency, other mitochondrial defects, lysinuric protein intolerance, and citrin deficiency may also be presented with hyperammonemia [1].

Bedside differential diagnosis of IEM presenting with hyperammonemia should be based on acidosis, ketonuria, hypoglycemia, the elevation of lactate acid, increases of aminotransferases, creatin-kinase, or uric acid, changes of complete blood count, and weight loss [4].

Genetic testing is used to confirm the diagnosis of UCDs and differentiate between CPS1 and NAGS deficiency. Once a genetic mutation is confirmed, prenatal diagnosis and family counseling are possible [2,7]. Recently, genetic testing is readily available and affordable for our patients suspected of UCD or other IEM with hyperammonemia.

Treatment

Both ammonia level and the clinical presentation should be considered when therapy is chosen. The neonates with symptomatic hyperammonemia should be transferred as soon as possible to a unit with possibilities for hemodialysis. The cerebral edema and neurologic complications are severe if ammonia could not be effectively cleared [7].

Emergency treatment to reduce the ammonia level should be initiated as quickly as possible and includes:

- Stop protein intake (temporarily, for a maximum of 24-48 hours),
- Start high caloric intake, orally (10-20% soluble glucose or protein-free formula) or intravenously (10% glucose by peripheral infusion or 20% glucose by central venous line); at least 110% of the recommended daily allowance,
- Ammonia scavenger: sodium benzoate, sodium phenylbutyrate (orally or intravenously),
- L-arginine (orally or intravenously),
- Hemodialysis, considered at an ammonia level of 300-500 µmol/L and strongly recommended when ammonia is over 500 µmol/L,
- Treatment for other conditions,
- Reduction of intracranial pressure,
- L-carnitine [3,4,8].

One of the most critical challenges for the physicians treating UCDs in our country is the lack of intravenous ammonia scavengers. Only the oral formulation of phenylbutyrate is registered in Romania since 2020. The option of hemodialysis in children is possible only in a few university hospitals. Because of this issue, children with hyperammonemia should be referred to such a center as quickly as possible.

Long-term treatment aims to obtain metabolic control and achieve normal development and growth, combining a low protein diet with a supplement of the essential amino acids, vitamins, trace elements, nitrogen scavengers, and other medications. Due to low palatability, volume and frequency of diet and medication, it represents a challenge to children and families. Only oral phenylbutyrate, arginine infusion, and carbamyl-glutamate are available for our patients from the guidelines list of possible drugs. A metabolic dietitian should be included in the team for the best results of nutritional treatment. If needed, early consideration of using tube feeding or gastrostomy feeding may help to adequate nutrition and administration of medication [2,4].

During an event with the risk of hyperammonemia, immediate action should be taken. A written treatment protocol should be included in an emergency plan with the needed steps in the acute management and dosage of different medications, updated to the children growing. It will help the effective and immediate treatment in emergency rooms. Also, the parents should be aware of the adjustment to the protein intake (reduced temporarily for 24-48 hours), increasing non-protein caloric input, and adjusting medication dosage during intercurrent illnesses to prevent hospitalization in self-limited diseases [1]. Ibuprofen is preferred over acetaminophen due to the liver toxicity of the latter. Caution when using antiemetics; may mask the signs of hyperammonemia [7].

Liver transplantation is indicated in severe UCD, liver cirrhosis in ASS, or children with recurrent symptomatic hyperammonemia, without sufficient response to standard treatment and low quality of life but without neurological damage [4,7]. It is the only curative treatment, as it replaces the complete urea cycle in the liver, but other cell types that express ASL are not corrected [5]. Survival rates now reach 95% at 1 year and 90% at 5 years [4].

Psychological support is an essential component of the care in UCD at any age, both to help to cope with anxiety or other psychological problems and to assess the cognitive status and neuropsychological function [4,7].

Prognosis of UCD is poor in children with ammonia levels over 1000 µmol/L, and intracranial pressure increased or coma longer than 3 days. In these cases, there could be a severe neurodevelopmental outcome [4,5,8].

Novel therapies are possible for hyperammonemia. Therapeutic hypothermia was proposed as a solution to control intracranial pressure in ALF with hyperammonemia. Recent studies included patients with UCD and isovaleric acidemia to prove the feasibility of this adjunct therapy. N-Carbamyl-L-glutamate, as a synthetic analog of

N-acetyl glutamate, may reduce ammonia level in NAGS deficiency and is licensed to treat hyperammonemia in three organic acidurias (MMA, PA, and IVA). L-ornithine-L-aspartate may enhance the urea cycle in residual hepatocytes and was tried in cirrhotic patients. Flumazenil has an anti-GABAergic activity and may be considered in some patients with chronic liver disease and hepatic encephalopathy. Gene therapy is studied for OTC in adults with late-onset. On animal models, the enzymatic activity and control of ammonia level were demonstrated [7]. Enzyme replacement therapy was researched for ARG1D [4]. Cell therapy focuses on the possibility of populating the liver of UCD patients with functional hepatocytes as a bridge therapy for severe disease [1,5].

Conclusions

Hyperammonemia should be suspected in any neonate with sepsis without an apparent infection and in any child with neurologic symptoms. Adequate treatment should be initiated as quickly as possible to reduce the ammonia level and duration of possible coma, the most critical risk factors for death. There should be a multidisciplinary approach in managing these children to improve survival chances and the long-term quality of life. Improvements in medical awareness and administrative regulations are needed in Romania to correct and timely diagnose hyperammonemia and mainly urea cycle disorders in children.

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