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Urea Cycle Defects: A Challenge for Neonatologists in Limited Resource Settings

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Abstract

Urea cycle defects (UCD)are rare inborn errors of nitrogen detoxification/arginine synthesis. We described clinical course of male newborn, second in order, with enormous concentration of ammonia, 4000 μmol/l. The first child died in early neonatal period with diagnosis of "severe neonatal sepsis". Laboratory finding showed no metabolic acidosis, abnormal plasma amino acids, absence of citrulline and increased urinary orotic acid. Despite aggressive treatment including he modyafiltration, hydration with dextrose and salt, dietary regime without proteins, ammonia scavengers as sodium benzoate and arginine repletion, newborn developed severe encephalopathy, multiorgan failure and died on the sixth day following birth. Due to short and catastrophic course of UCD in neonatal period, there is a high possibility of misdiagnosis, especially differential to neonatal sepsis and prompt ammonia measurement is the crucial step. Identifying specific UCD is not available in many countries with limited resources. Laboratory parameters will guide the diagnostic workup of a patient with hyperammonemia for which a specific diagnosis is yet unclear. Since the molecular genetic testing is the method of first choice, in order to confirm the diagnosis it is necessary to preserve frozen fibroblasts and provide genetic counseling.

Keywords: Hyperammonemia, Urea cycle disorders, OTC deficiency

Introduction

Hyperammonemia is usually defined as a plasmatic level of ammonia above 80 μmol/L in infants up to 1 month of age,and above 55 μmol/L in older children. (1) It is an acute life-threatening condition that can lead to severe neurologic impairment and cerebral edema. Multiples diseases can lead to acute hyperammonemia in children admitted in pediatric intensive care: liver failure, inborn error of methabolism (IEM), such as Urea Cycle Defects (UCDs), organic academies, fatty acids oxidations disorders,exposure to toxins and medications.IEM can be the most difficult to recognize, given an overall prevalence at approximately 10–15 in every 100,000 births.The prevalence of UDCs may exceed the current estimation of1:8,000-1:44,000 births (for all UCDs jointly) because of unreliable newborn screening and underdiagnosis of fatal cases. (2-6)

The classic presentation of neonatal hyperammonemia is as a catastrophic illness in the first week of life. Signs and symptoms of hyperammonia in the neonate depend on the proximate cause and the rapidity of ammonia accumulation. In patients with rapidly accumulating ammonia, presentation may occur in the first 2–3 days of life with lethargy, poor feeding, vomiting, tachypnea, seizures. This may progress over a matter of hours to temperature instability, coma, and evidence of increased intracranial pressure. (7,8,9) UCDs are inborn errors of nitrogen detoxification/arginine synthesis due to defects in the urea cycle enzymes including deficiency of carbamoyl phosphate synthetase 1 (CPS1), ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), argininosuccinate lyase (ASL) and arginase 1 (ARG1). They also encompass deficiencies of N-acetylglutamate synthase (NAGS), associated with lack of the N-acetylglutamate (NAG) essential activator of CPS1 and of the mitochondrial ornithine/citrulline antiporter (ORNT1).(2,8,9,10)

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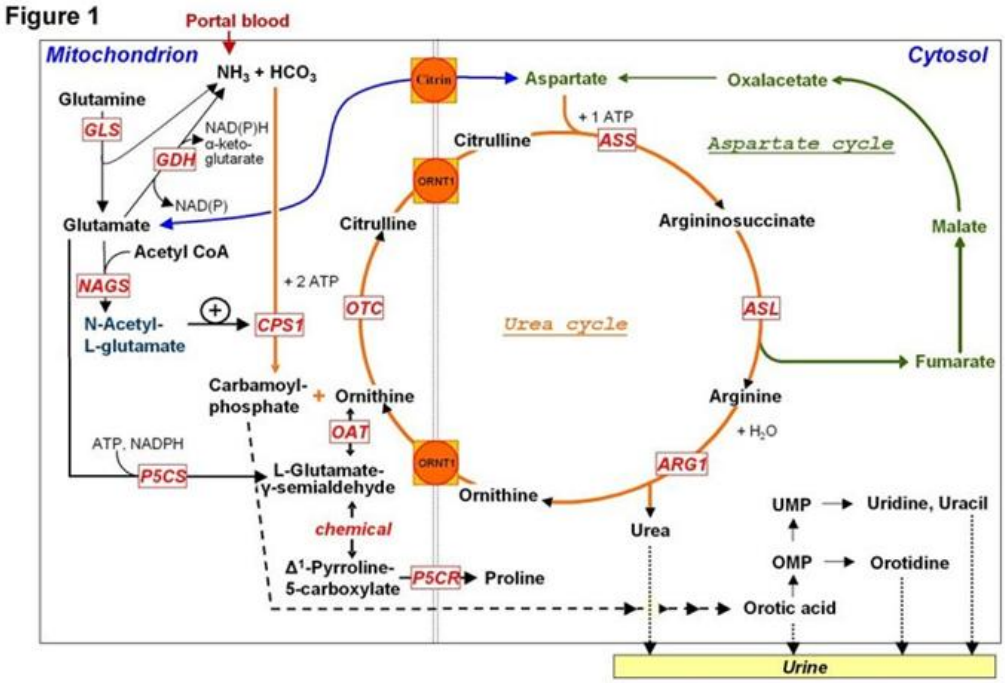
The most common inherited defect of ureagenesis (>50% of all UCDs) is OTC deficiency, with a prevalence of 1 for 14,000 to 1 for 62,000–77,000 live births. (1,7,11) OTC deficiency is an X-linked disorder. In males, OTC is usually lethal in the neonatal period, although milder variants are also described. In females, there is a wide variability of symptoms due to the X-inactivation pattern with 15-20% more severe symptoms. (1,11)

The urea cycle and associated pathways



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Case report

This is a case report of a male newborn, born as the second child in order, from the mother's second marriage. First child(from the first marriage), also male, died in the early neonatal period (mother kept this secret) with diagnose of "severe neonatal sepsis", with encephalopathy, seizures, coma and multiorgan failure. This pregnancy was uneventful, and the baby was born by vaginal delivery, BW 3500 g, API 10/10, discharged from the hospital as healthy in the second postnatal day. Clinical manifestation of the illness started approximately 60 hours after birth with sepsis like picture, including poor feeding, lethargy, respiratory distress, hypothermia, abnormal body posturing. Baby was immediately admitted to the hospital. Clinical manifestation was rapidly getting worse, with altered level of consciousness, 72 hours after birth child is irresponsible, and seizures are registered. After the respiratory arrest happened baby was immediately in to bated and placed on mechanical ventilation, phenobarbital and empiric antibiotics were given.

Newborn laboratory screening is made: Blood gases showed tendency toward respiratory alkalosis; blood glucose, serum electrolytes, bicarbonate, CRP, BUN, creatinine, bilirubin, plasma lactic acid, ketones in urine and liver function tests were unremarkable (AST, ALT slightly elevated). Blood, cerebrospinal and urine cultures are taken (negative). Plasma ammonia measurement showed enormousconcertation of ammonia – 4000 μmol/l. Brain ultrasound showedsymmetric increased echogenicity of the periventricular white matter and thalami. Ultrasound of heart and abdomen were unremarkable. EEG finding have showedincreasedepileptically activity above both brain hemispheres. Due to enormous blood ammonia level, blood and urine samples were urgently sent to Clinical Center Rebro, Zagreb to perform prompt quantitative serum amino acid analysis and urine organic acid analysis, since those analyses could not be done in our institution. In the same time fibroblasts preserved frozen for the DNA isolation.

NALAZ AMINOKISELINA u plazmi

Aminokiseline	Koncentracija (μmol/L)	Referentni raspon novorođenčad (μmol/L)
Fosfoserin	6	1-47
Taurin	32	40-265
Fosfoetanolamin	17	3-27
Asparaginska kiselina	7	0-20
Hidroksiprolin	0	0-80
Treonin	66	90-329
Serin	45	94-360
Asparagin	81	30-132
Glutaminska kiselina	10	30-110
Glutamin	1890	370-958
Alfa-aminoadipinska kiselina	0	0
Prolin	160	107-330
Glicin	230	224-514
Alanin	339	131-460
Citrulin	0	9-35
Alfa-aminomaslačna kiselina	7	6-30
Valin	87	80-210
Cistin	10	17-84
Cistationin	0	0-3
Metionin	52	15-50
Isoleucin	29	26-80
Leucin	72	46-160
Tirozin	67	42-135
Fenilalanin	61	38-120
Homocistin	0	0
Beta-alanin	0	0-15
Beta-aminoizomaslačna kiselina	0	0
GABA	0	0-2
Histidin	77	30-125
3-Metilhistidin	3	0-5
1-Methilhistidin	0	0-43
Triptofan	-	0-60
Homokarnosin	0	0-19
Ornitin	29	48-210
Lisin	221	92-310
Arginin	18	6-130

Results showed very high plasma glutamin level and absence (extremely low, immeasurable) citrulin level. This result, including relatively low arginin level indicate urea cycle defect (OTC deficiency, NAGS deficiency or CP deficiency). Alanin concentration is in normal range. Urine organic acid analysis by gas chromatography showed increased concentration of orotic acid, which is highly suggestive of OTC deficiency. Positive familiar anamnesis (previous neonatal death) is confirmed, genetic molecular testing is recommended and lately confirmed by identifying DNA mutation.

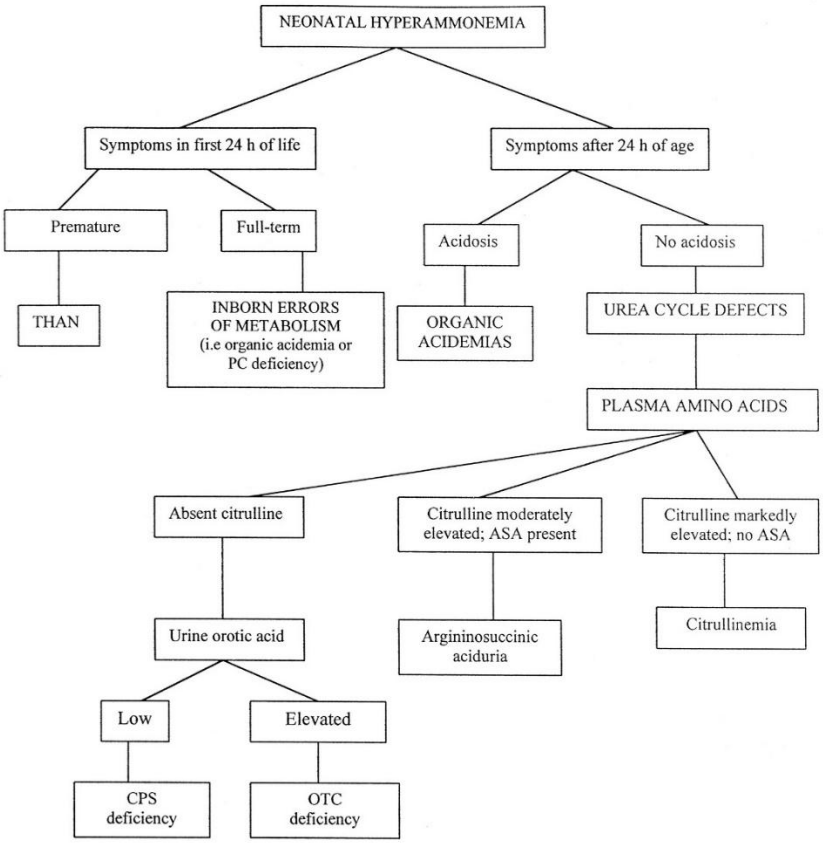
After hyperammonemia is confirmed, hemo(dia)filtration isimmediately organized in cooperation with pediatric nephrologist and ammonia concentration was reduced to 1330 μmol/l, than varies maintaining concentrations between 150-300 μmol/l. All protein intake is stopped. Intravenous fluids with dextrose, salt and intralipidsare given to provide 120-130 kcal/kg/day through a central line,as well assodium benzoate as ammonia scavenger medicationsandsupplemental arginine which may be deficient due to early enzymatic blocks and to stimulate the urea cycle.

Despite all treatment the child developed multiorgan failurewith the lethal outcome on sixth postnatal day. Insight into medical documentation of the first child, revealed the similar clinical course with death outcome in fourth postnatal day.

Discussion

When hyperammonemia is present in the newborn period, an attempt to identify a diagnosis is essential. A number of conditions that increase ammonia production and/or secondarily decrease ammonia detoxification can cause hyperammonemia and mimic a UCD. (12,13,14) The most common misdiagnosis of early onset UCD patients is neonatal sepsis (12).Risk factors are consanguinity and previous deaths in family. A systematic approach for the differential diagnosis of hyperammonemia is needed. Guideline for the diagnosis and management of urea cycle disorders is developed by the Guideline Development Group (GDG) (2) and recently revised. (12)

Guidelines for the diagnosis and management of urea cycle disorders



From Burton B. (14)

It is very important to remember that the first step in evaluating suspected hyperammonemia is to obtain an accurate blood ammonia level. (15,16) Since the newborn expressed hyperammonemia following latent period longer than 24 hours, secondary hyperammonemia such as a pyruvate carboxylase deficiency (PCD) and transient hyperammonemia of preterm newborns (THAN)can be excluded with great certainty. (14) Hyperammonemia after the first 24 hours following birth is more characteristic of a primary hyperammonemia, which includes mainly urea cycle defects, organic acidemias and fatty acid oxidation disorders. The key to differentiation is the presence or absence of acidosis, ketosis and hypoglycemia. The urea cycle defects usually present with respiratory alkalosis due to the hyperpnea, induced by the hyperammonemia, the absence of hypoglycemia in contrast of classical presentation of fatty acid oxidation disorders with nonketotic and ketotic hypoglycemia with acidosis, typical for PCD in addition to organic acidemias. (16)

Among urea cycle disorders OTC deficiency is the most prevalent. (2,17) Due to its X-linked nature, parental consanguinity is uncommon and males are more frequently affected.The laboratory evaluation includes the quantitative analysis of plasma amino acid by high performance liquid chromatography and urine organic acids/urine orotic acid analyses. (3,12,18) If citrulline is absent or decreased, urine orotic acid will differentiate between NAGS, CPS, and OTC deficiency. In NAGS and CPS, the urine orotic acid will be low; while in OTC it is elevated. (12,17,18).Diagnosis is confirmed by identifying the mutation in DNA, an approach that permits detecting carrier females and affected fetuses.(19)

Neonates with profound and prolonged hyperammonemia with coma due to urea cycle defect will have had a neurological insult to the brain that may be significant. If so, the option of withdrawal of support rather than aggressive intervention should be discussed with the parents. (19) Even with aggressive intervention, including hemodyalisis in acute phase, many will die. The therapy is multifocused, including the removal of the accumulating metabolites, hydration, adequate caloric intake, drug therapy,as sodium benzoat to provide an alternative path for nitrogen excretion and arginin repletition. (1,3,6,18,20,21)

The overall prognosis for newborns with a urea cycle defect is guarded. Those newborns that do survive may have neurological insult and recurrent life-threatening metabolic crises.With advances in liver transplantation, the indications for liver transplantation for urea cycle defects are changing. (22) Gene therapy is field of research that could provide the potential to reduce the morbidity and mortality seen in urea cycle defects. (23,24)

Conclusion

Due to short and catastrophic course of UCD in neonatal period, there is a high possibility of misdiagnosis, especially differential to neonatal sepsis, so the prompt ammonia measurement is the crucial step. Identifying specific UCD is not available in many countries with limited resources. Laboratory parameters will guide the diagnostic workup of a patient with hyperammonemia for which a specific diagnosis is yet unclear. Since the molecular genetic testing is the method of first choice to confirm the diagnosis fibroblasts should be preserved frozen and genetic counselling is necessary.

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