

Clinical and genetic diversity of congenital hyperammonemia

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Abstract

Congenital hyperammonemia (HA) due to inborn errors of metabolism is a rare condition with a high rate of mortality. The main effects occur at the central nervous system (CNS) level, being neurotoxic by alteration of the neurotransmitter function. HA can be triggered by an inappropriate diet, infection or stress, but can also occur without a precise cause. In cases of metabolic crises, patients require immediately intensive care. In the last seven years (2011–2017), we cared in the Department of Genetics, "Dr. Gavril Curteanu" Municipal Clinical Hospital, Oradea, Romania, six patients with different causes of congenital HA: one case with argininosuccinate lyase deficiency, two cases (brothers) with argininosuccinate synthase deficiency, one case with non-ketotic hyperglycinemia, one case hyperglycinemia and one case with HA with unknown etiology. The medical surveillance and care of these children over a long period of time raise serious problems for the family and society. These patients are dependent on medical services: qualified medical staff (pediatrician, geneticist, radiologist, biochemist, nutritionist, and psychologist), expensive and repeated medical investigations, prolonged and costly medication. Most of these costs could be avoided by early diagnosis and treatment, rigorous monitoring of HA, ensuring proper diet and medication. Our experience regarding the clinical and genetic particularities of patients with congenital HA could be an opportunity for the better knowledge of special needs of these patients, especially regarding the psychological and social aspects.

Keywords: congenital hyperammonemia, central nervous system, inborn errors of metabolism.

Introduction

Hyperammonemia (HA) is a life-threatening condition caused by various acquired disorders (especially severe hepatic diseases) or inherited disorders (especially urea cycle deficiencies or organic acidemias). Ammonia is a neurotoxic substance, which explains why most clinical sequels affect the central nervous system. Neurological features due to HA include cortical atrophy, ventricular dilatation and demyelination [1]. It also determines changes in behavior, seizures, coma and, as long-term, neurological and intellectual disability [2]. Any delay in recognition and/or beginning of treatment of HA can induce deleterious consequences for the patient [3, 4]. When a newborn is diagnosed with HA, family life is changed forever. The parents must accept a different life than they have imagined. To deal with these problems, parents need the support available from all family members, relatives or friends. At the moment of diagnosis, the parents react differently, some of them hardly accepting the diagnosis of HA. Many problems arise in connection with the diet and with the medical treatment. There is a permanent fear of the parents because of the risk of occurrence of the HA crisis. These crises may be induced by an incorrect diet, certain infections, but they can also occur without a precise cause. During the HA crisis, patients require emergency hospitalization and intensive care. However, the sudden onset of HA episodes endangers life

and can cause organopathic changes especially in the central nervous system [5, 6]. Our paper focuses on clinical monitoring of patients with HA as well as genetic aspects. Medical observation and care of these children over a long period raise serious problems for the family and society.

Case presentations

We present a short synthetic clinical description as well as the psychosocial aspects in connection with six patients diagnosed with congenital HA, observed for a period of seven years in the Department of Genetics, "Dr. Gavril Curteanu" Municipal Clinical Hospital, Oradea, Romania. We discuss particular clinical and genetic diversity and psychosocial aspect of each case as well as general issues of all patients.

Case No. 1

A boy, five years and three months old, was the fourth child of young, healthy and non-consanguineous parents. He was born in 2012 at 37 weeks gestational age, with the weight 2860 g and without perinatal incidents. Previously, three live sisters have died in the first 12 days of life, all with the same clinical evolution: seizures, coma, multi-systemic hemorrhages, death. No causal diagnosis was known. From the third day of life, the boy showed marked somnolence, myoclonus, hepatomegaly, coma. Physical

examination showed normal somatic phenotype. Laboratory investigations shown very high values of serum ammonemia 945 $\mu\text{mol/L}$ (reference values: 16–60 $\mu\text{mol/L}$). The metabolic screening for inborn errors of metabolism revealed argininosuccinate lyase deficiency (argininosuccinic aciduria), neonatal form. Clinical evolution, under the complex treatment (parenteral nutrition, hemodialysis, ammonia scavengers), was generally favorable. He continued chronic treatment consisting of low-protein, normolipidic, normoglycemic, and normocaloric diet and ammonia scavengers. Growth is normal, but psychomotor development is moderately delayed.

Cases No. 2 and No. 3

Two brothers with young parents, affirmatively healthy, at first marriage, non-related. They had two boys, both born at 40 weeks gestational age in 2011, respectively 2015. Physiological pregnancy, spontaneous delivery, normal weight, good adaptation to the extrauterine life. Both brothers have not genetic somatic markers on physical examination. From the second day of life, both boys presented somnolence, vomiting, tachypnea, seizures, coma. Laboratory investigations shows mild metabolic alkalosis, high levels of ammonia (524 $\mu\text{mol/L}$ and 611 $\mu\text{mol/L}$, respectively). The metabolic screening has revealed argininosuccinate-synthase deficiency (type I citrulinemia). In the Case No. 2, the treatment consisted of anticonvulsant drugs and supportive (glucose and electrolytes) but the evolution was with persistent coma and death at age of five days. His brother (Case No. 3) survived the acute episode of seizures and coma from the first week of life and received chronic treatment with ammonia scavengers (Sodium Benzoate and Sodium Phenylbutyrate), low protein milk formula, and supplementation with L-Carnitine and L-Arginine. The clinical evolution was unsatisfactory, with failure to thrive and death in the third month of life.

Case No. 4

The patient is a three-year-old boy (born 2013) with young and healthy parents, no consanguineous. Mother's obstetrical history revealed two spontaneous abortions at gestational age of six and 10 weeks, respectively. The patient comes from the second pregnancy of the mother. The first pregnancy was a boy born premature at 29–30 gestational weeks, who died at the age of seven days by neonatal sepsis, hyaline membrane disease. The pregnancy had a pathological evolution with imminence of abortion. The onset of symptoms was in the fifth day of life with spontaneous cyanosis crises, seizures, accompanied by generalized hypertonia. Phenotypically, there was a slight craniofacial dysmorphism: left ear position asymmetry with the lower left ear compared to the right ear, micrognathia. Laboratory investigations revealed HA at level of 100 $\mu\text{mol/L}$, suggesting an inborn error of metabolism. Transfontanelar ultrasound (US) and brain magnetic resonance imaging (MRI) do not reveal pathological elements. Cardiologic exam and echocardiography does not reveal cardiovascular abnormalities. Dosage of plasma amino acids revealed elevated serum glycine, 2.4 mg/dL (reference values: 0.8–1.1 mg/dL). Based on the clinical picture and biochemistry data, a diagnosis of congenital non-ketotic hyperglycinemia with secondary HA was

established. After the treatment of acute episode with ammonia scavengers (Sodium Benzoate), L-Arginine, anticonvulsant drugs, the chronic treatment of HA was made with hypoproteic diet. Clinical evolution under treatment was favorable, the growth and development being normal.

Case No. 5

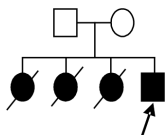
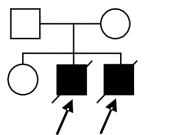
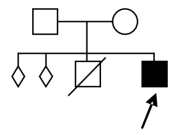
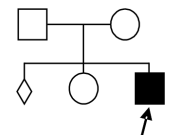
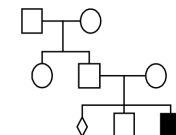
Boy, four years and eight months, born in 2013; young, healthy parents, without known inbreeding. This was the mother's third pregnancy after a spontaneous abortion and birth of a normal girl. The pregnancy was normal. No known perinatal incidents. At the age of three weeks, he presented some repeated apnea crises; there was an unsatisfactory progression of apnea crises associated with myoclonus, coma, generalized hypotonic syndrome. Phenotypically, the patient showed a craniofacial dysmorphism with high forehead, height hair insertion with coarse hair, downslanting palpebral fissures, hypertelorism, deep nasal root. Laboratory investigations revealed increased ammonia (198 $\mu\text{mol/L}$). Metabolic screening showed high values of glycine (1.8 mg/dL). No organic urinary acids have been identified. Cardiologic examination and electrocardiography were normal. Neurological examination show marked hypotonia, flaccid turgor, hyporesponsive facies with frequent critical manifestations, polymorphs, myoclonus, apneiform manifestations, generalized tonic seizures. Electroencephalography show rare slow path. Brain computed tomography (CT) was normal. The diagnosis was for unspecified metabolic encephalopathy with HA. The treatment was with anticonvulsants drugs, L-Arginine, low protein intake. Clinical evolution of the patient was generally favorable, without apnea and myoclonus episodes, less marked hypotonia. A moderate delay has been observed in somatic and psychomotor development.

Case No. 6

Boy aged five years and five months (born in 2012); young and healthy parents, without known inbreeding. The boy is the second child in the family. The mother had previously a spontaneous abortion and a healthy boy. The boy's father, paternal grandmother and a father's sister have an undetermined morphological anomaly (dwarfism with major deformation of the spinal cord, osteochondrodysplasia). From the second day of life, he presented generalized convulsions. Phenotypically he presented a craniofacial dysmorphism: plagiocephaly, hypertelorism, nose with bevelled root, small mouth, without other genetic somatic markers. Laboratory investigations revealed HA (184 $\mu\text{mol/L}$). The metabolic screening was normal. Brain CT revealed cerebral edema, mild cerebral atrophy. Neurological examination showed marked hypotonia, severe neuropsychomotor retardation. The initial treatment was with anticonvulsants drugs, associated with ammonia scavengers (Sodium Benzoate), L-Arginine, L-Carnitine. Clinical evolution has been connected with the reduction of seizure episodes, being maintained a severe neuropsychomotor delay.

We do a clinical presentation of our cases, then a synthesis of the main clinical and laboratory data (Table 1).

Table 1 – Synthesis of clinical and laboratory data of six patients with congenital HA

	Case No. 1	Cases No. 2 and No. 3	Case No. 4	Case No. 5	Case No. 6
Family history					
Age of onset	First day of the life	Each case in the first day of the life	Five days	Three weeks	Two days
Clinical symptoms	Seizures, coma, tachypnea	Seizures, coma, tachypnea	Seizures, coma, cyanosis	Apnea crisis	Seizures, tachypnea
Ammonium level	945 µmol/L	Case No. 2: 524 µmol/L Case No. 3: 611 µmol/L	100 µmol/L	198 µmol/L	184 µmol/L
Screening for inborn errors of metabolism	Argininosuccinate lyase deficiency (argininosuccinic aciduria)	Argininosuccinate synthetase deficiency (type I citrulinemia)	Glycinemia ↑ Serinemia ↑ (non-ketotic hyperglycinemia)	Valinemia ↑ Tyrosinemia ↑ Threoninemia ↑ Glycinemia ↑	Negative
Evolution	Recurrent episodes of seizures and coma; mental and neuromotor deficiency	Case No. 2: Coma, death at age of five days Case No. 3: Death in the third month of life	Favorable, without seizures	Seizures (periodic); severe neuromotor deficiency	Frequent episodes of seizures; neuromotor deficiency; marked hypotonia
Treatment	Hemodialysis Anticonvulsant therapy Nitrogen scavengers (Sodium Benzoate and Sodium Phenylbutyrate) L-Arginine L-Carnitine Protein restriction	Case No. 2: Anticonvulsant therapy Case No. 3: Nitrogen scavengers (Sodium Benzoate and Sodium Phenylbutyrate) L-Arginine L-Carnitine Protein restriction	Nitrogen scavengers (Sodium Benzoate) Anticonvulsant therapy L-Arginine L-Carnitine Protein restriction	Anticonvulsant therapy Protein restriction	Nitrogen scavengers (Sodium Benzoate) L-Arginine L-Carnitine Protein restriction

HA: Hyperammonemia.

Discussions

From Table 1, it can be noted that in all cases there is a familial genetic load, other people being affected with the same disease (in two families) or positive history for abortion or perinatal deaths. Usually, the onset of symptoms is in the early days of life, but there are forms with late onset, too (Case No. 5). Common symptoms at onset are seizures, coma and respiratory signs. Death can occur frequently in neonatal forms of HA as can be seen in our series. In the first case, there were three newborns, all with the same symptoms, all died in the early days. Unfortunately, we have not more clinical or biochemical information about them but is very likely to consider them having the same disorder. In survival, clinical outcome depends on the precocity of treatment and on compliance with treatment.

In a large meta-analytic study, Zeltner *et al.* (2014) [5] concludes that inborn errors of metabolism, including urea cycle disorders, which have severe clinical manifestation during the first few days of life, are at increased risk for having psychosocial problems throughout life (social adjustment, anxiety, depression, intellectual disability, behavioral difficulties) [7, 8]. The clinical forms with late diagnosis are also at risk to develop progressive psychiatric delay because of chronic ammonia intoxication.

HA values (repeated) are variable from 2–3 times to 20–30 times higher than the reference values. Elevated and persistent values represent aggravating circumstances for neurological development. Evolution without treatment is usually fatal. Early diagnosis, correct monitoring of HA and the adjustments to appropriate therapy improve significantly the prognosis.

HA has been suggested, at the four cases with neonatal

onset, by neurological and respiratory signs: seizures, coma, tachypnea, and apnea. No morphopathological or dysmorphic abnormalities were associated [9, 10].

Along of the evolution, the level of HA is oscillating but permanent. Acute episodes may occur after inadvertent protein ingestion or hypercatabolic states (infections, trauma, and drugs). Without treatment, the evolution is usually fatal. Early diagnosis, correct monitoring of HA and the adjustments to appropriate therapy improve prognosis significantly.

The diagnosis of inborn errors of metabolism responsible for congenital HA is hardly accepted by the family because of minimum two reasons: first, the negative family history (usually, no other affected peoples in the family), second, no somatic abnormalities are visible. Different persons react in different ways when they find out the diagnosis. In most cases, there are changes in interpersonal relationships, opinion conflicts, parents feel guilty, sometimes with mutual accusations that can lead to family breakdown. It is very important how the doctor communicate the final diagnosis, directly to patients or to others family members. A good communication between physician and family is essential to provide the best conditions for child development [11, 12].

It is proven that finding other families with the same diagnosis, contacting parent organizations, talking to people with the same experience in the same situation becomes very useful for parents in order to find ways to overcome and cope with this painful situation.

The medical supervision and care of these children over a long period of time (years or decades) poses serious social problems for the family and society. A large number of these patients are dependent and they need a permanent accompanying person. They need a special care, extra cost

for food, education, medical consumption (qualified staff, repeated investigations, prolonged and costly medication, etc.). Most of these costs could be avoided by early diagnosis and treatment, rigorous monitoring of HA, ensuring proper diet and medication [13].

HA patients should be monitored and evaluated throughout their lives. Due to dietetic deprivation there is a risk of protein or/and vitamin deficiencies. Therefore, long-term monitoring is needed to prevent delays in development, growth and head circumference, neuro-cognitive development and liver size and structure (by ultrasound scan) [14–16]. The clinical and biochemical control should be individualized at regular intervals, depending metabolic stability and compliance with diet and drug therapy. Regular dietary evaluations are also essential, and the diet should be adjusted for age and growth [17, 18].

☒ Conclusions

Early diagnosis and early initiation of treatment are essential for the prevention of immediate and late complications of congenital HA. Neonatal selective or non-selective screening is the ideal solution for early diagnosis. Long-term management must aim, besides a rigorous control of the disease, social protection and psychological adjustment, assuring a good quality of life.

Conflict of interests

The authors declare that they have no conflict of interests.

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