The Case of the Non-Ketotic Hyperglycinemia at 1,5 Years Girl in the Republic of Kazakhstan

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Abstract

Non-ketotic hyperglycinemia (NKH) is a rare, inherited disease with very poor outcome. It is difficult to confirm the diagnosis due to nonspecific presentations and rapid progression. The incidence was reported in a few countries [1]. The overall incidence of non-ketotic hyperglycinemia is unknown but is higher in certain populations such as north Finland (1/12,000) and British Colombia (1/63,000). Three genes (GLDC, AMT and GCSH) are known to cause non-ketotic hyperglycinemia [2]. We report about first diagnosed case in the Republic of Kazakhstan. Furthermore, this study aimed to increase the alertness of pediatricians to possibility of meeting with this disease. We present the case-report of the NKH in the Republic of Kazakhstan.

Keywords: Glycine Decarboxylase Gene (GLDC); Non-Ketotic Hyperglycinemia; Seizure; Neonatal Encephalopathy; Inborn Error of Metabolism

Introduction

Non-ketotic hyperglycinemia (NKH) is an autosomal-recessive inborn error of glycine metabolism, resulting in the accumulation of large amounts of glycine in body fluids and severe neurologic disturbances immediately after birth [1].

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This metabolic disorder is due to a defect in the liver enzyme complex, termed the glycine cleavage system. Although GLDC (glycine decarboxylase) gene mutation had been known the most seen mutation [2]. The majority of NKH patients have a specific defect in P-protein (glycine decarboxylase). The primary lesion of NKH at gene level was investigated, using cDNA encoding human glycine decarboxylase. Recent findings suggest that a high concentration of glycine in the brain may contribute to the pathophysiology of NKH by overactivating N-methyl-d-aspartate receptors allosterically, which may result in intracellular calcium accumulation, DNA fragmentation and neuronal death [3]. Clinical manifestation accompanies by lethargy, progressive apnea and signs of the neonatal encephalopathy. Most of published cases have similar clinical features such as lethargy, intractable seizures or burst suppression pattern on EEG and elevated CSF/Plasma Glycine ratio (> 0.08) [2]. Prenatal diagnosis is feasible by determining the activity of the glycine cleavage system and also possible by DNA analysis [3]. Our case is a first diagnosed in the Republic of Kazakhstan. We also described possible causes of problematic diagnosing of the NKH.

The female infant patient was born at 41 weeks gestation, weight is 3280 grams, and height is 55 centimeters. On the next day after delivery she was transferred to the Intensive care unit with a coma and cyanosis. In 5 minutes after delivery the APGAR score was 8 therefore there is no hypoxia. Seizures started from second day of life as tonic convulsions and cyanosis. After 7 days she was transferred to the National Research Center for Maternity and Childhood (NRMCCH) to NICU: suspicious for bacterial sepsis, neonatal pneumonia, epileptic encephalopathy, early myoclonic epilepsy. The clinical manifestation was accompanied by lethargy and progressive apnea. She spent 30 day on artificial ventilation. At the age of 7 months she was hospitalized with tonic-clonic seizures lasting up to 1.5 hours. The next attack was at night during sleep lasting up to 5 minutes in the form of fading, vomiting, tonic-clonic seizures of the upper and lower extremities, tilting the head to the left. At the age of 9 months she was admitted to the hospital again with epileptic encephalopathy, epileptic spasms (with a suspicion of the genetic nature of the disease).

At the age of 1 year 4 months instrumental research methods was performed brain MRI and EEG. MRI demonstrates diffuse glial-atrophic changes, post-hypoxic changes at white matter, assymetric enlargement of lateral ventricles with slight hypogenesis of the corpus callosum (Figure 1). In patient with NKH MRI shows heterogeneous brain malformations, such as abnormal corpus callosum, gyral malformations and enlarged ventricles [4,5]. EEG indicated slow wave activity at background, multifocal, asynchronous, asymmetric, sharp wave activity with some spikes at left temporal region. There are areas of the burst suppression pattern in the right brain regions are recorded (Figure 2). The typical presentation of EEG is burst suppression, which often evolves into hypsarrhythmia or multifocal spikes and sharp waves [6].

Figure 1: Magnetic resonance signs of diffuse glial-atrophic changes, post-hypoxic changes in the substance of the cerebral hemispheres. Assymetry, combined hydrocephalus. Hypogenesis of the corpus callosum.

At the age of 1 year 7 months molecular genetic analysis and amino acid profile were performed. Molecular genetic analysis was performed by sequencing of Glycine decarboxylase (GLDC) gene. Here we found a mutation (c.830C > A p. (Thr277Lys), c.1841A > C p. (Gln614Pro)) of the GLDC gene (NM_000170.2). The result is compatible with glycine encephalopathy. Both parents are heterozygous, asymptomatic. The patient’s homozygous status is confirmed. Both homozygous variants of the GLDC gene were detected. The amino acid profile confirmed the increase level of glycine up to 1097 mmol/L.

Clinically she developed apneic episodes, lethargy and was then intubated and ventilated. Neurological status in clinical manifestation: the state of a child is severe, convulsive syndrome. Obvious delay in psychomotor development, there are hyperkinesis, dystonic attacks, pronounced hypotrophy, emotional reactions are reduced, the eyes does not fix, does not smile, does not stretch to the toys. Diet before diagnosis was not applied and was not adjusted. She was treated by several AED: Phenobarbital since six days of life for arresting seizures, transition to Valproate initial dosage 10 mg/kg (Convulex 2 drops/2 times) with increasing dose up to 30 mg/kg/day (at the age of one month, weight 4 kg). Because of the ineffectiveness of the drug at the age of 7 months (weight 7 kg) was transferred to Keppra with an increase in the dose of 120 mg/2 times a day, Trihexyphenidyl 2 mg for 1/6 tablets /3 times a day. Further, she received treatment for drugs: Valproate (switched to Depakine 50 mg/50 mg/100 mg during the day (30 mg/kg/day), Topamax 1.7 mg/kg/day. The condition after anticonvulsant therapy has slightly improved. Hyperkinesis decreased. The patient became calmer. The sleep has greatly improved. Convulsions of a tonic character decreased to 20 times a day to 2 minutes. However, the muscle tone in all the limbs is increased. Tendon reflexes in the upper and lower extremities are increased with the expansion of the reflexogenic zones. Finally after molecular genetic analysis and diagnosis of non-ketogenic hyperglycinemia, a ketogenic diet (2:2:1) was prescribed (at the age of 2,1 years old). The patient’s condition after the ketogenic diet has improved for two months. The neurologic status improved markedly for first two months. The frequency of convulsions of a tonic character decreased to 3 times a day. but weight was a stable (8,5 kg, the deficit of body weight was 50%). After two months of ketogenic diet patient become letargic again.
**Discussion**

According to clinical, laboratory data she was diagnosed as a non-ketotic hyperglycinemia. Inefficient traditional anticonvulsant treatment, results of laboratory-instrumental studies (molecular genetic analysis, amino acid profile, EEG, MRI) and the clinical data of this patient (lethargy, convulsions, encephalopathy, and hepatomegaly) correspond to the clinical manifestation of non-ketotic hyperglycinemia, which refers to glycine encephalopathies. According to the literature, there is no etiological treatment. Pathogenic therapy consists of integrated approach of 3 interventions: ketogenic diet, sodium benzoate and imipramine.

Nowadays, it’s not possible to put the correct diagnosis by one examination therefore the status evaluation should be carried out in dynamics. Diagnostic search for glycine encephalopathy can be prolonged for a long time. Therefore, it is necessary to pay special attention to the diagnostic criteria of this disease. A small spectrum of screening for metabolic pathologies does not able reveal metabolic disorders such as NKH. There is a problem of diagnosis and examination of patients with metabolic disorders. Neonatal screening of metabolic pathologies in Kazakhstan includes only 2 diseases: Phenylketonuria (PKU) and hypothyroidism, while in other countries neonatal screening program includes more than 30 different metabolic conditions. The case of misdiagnosing of bacterial sepsis became common in practice. Therefore, the patient undergoes non-effective therapy while she needs timely diagnosis and adequate care.

**Conclusion**

Due to the absence of molecular genetic analysis in the Republic of Kazakhstan, the diagnosis of NKH is problematic. This is confirmed by the fact that our patient is the first in the Republic of Kazakhstan who has been registered with the NKH. 8 grades on the APGAR scale indicates that the child did not experienced asphyxia and therefore lethargy and signs of neonatal encephalopathy at birth were very unclear and this is the reason to suspect a pathology other than hypoxic brain damage. This is the red flag in determining the tactics of the examining, namely the conduct of metabolic and genetic analysis.

The next step in the study will be the systematization of the available information on non-ketogenic hyperglycinemia, so that at the time of the initial examination, the disease can be quickly identified. Thus, the patient has more chances to receive adequate care in a timely manner.

**Bibliography**


