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NONKETOTIC HYPERGLYCINEMIA IN A NEWBORN INFANT*

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SUMMARY: Tekinalp G, Coşkun T, Oran O, Özalp İ, Figen G, Ergin H. (Neonatology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Nonketotic hyperglycinemia in a newborn infant. Turk J Pediatr 1995; 37: 57-60.

A neonate with nonketotic hyperglycinemia who experienced apnea, hiccups and tonic-clonic seizures on the first day of life is reported. The physical findings and laboratory tests including arterial blood gases were normal. However, serial blood and CSF aminoacid analyses demonstrated elevated glycine levels. Serum and CSF glycine levels were 1949 µmol/L and 415.5 µmol/L, respectively. (Normal serum level is 104-254 µmol/L and CSF level is 5 ± 2 µmol/L). The CSF/plasma glycine ratio was 0.11. Oral sodium benzoate and folic acid therapy was initiated. After two weeks of assisted ventilation and clinical improvement, the patient was discharged with a protein-restricted diet. *Key words: nonketotic hyperglycinemia, newborn.*

Nonketotic hyperglycinemia (NKH) is an inherited disorder of glycine metabolism characterized by abnormally high concentrations of glycine in plasma and cerebrospinal fluid (CSF) in the absence of excess organic acids[1,2]. NKH is caused by a defect in the glycine cleavage system (GCS)[2-5]. The clinical picture is variable and seems to relate to the degree of the defect in the GCS. Patients may have neonatal, infantile or late-onset phenotypes. Patients with the neonatal form of the disease either die within months of the initial examination or survive with severe mental retardation. Newborn infants develop rapidly progressing neurological symptoms such as muscular hypotonia, seizures, respiratory distress, persistent hiccups, lethargy or coma[3].

We present the clinical and laboratory findings of a case with neonatal-type NKH. To the best of our knowledge this is the second case report of its type from Turkey[6].

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Case Report

A one-day-old boy was admitted to Hacettepe University Children's Hospital Neonatal Intensive Care Unit because of previous sibling death. This infant was born at full term by cesarean section to a gravida 3, para 2, abortion 1 mother. His Apgar scores were 9 and 10 at one and five minutes, respectively. There was no consanguinity. One female sibling had earlier presented with extreme hypotonia, feeding difficulties and intractable seizures, and had died at the age of seventeen days.

On admission, the physical examination revealed a head circumference of 36.5 cm (90^{th} percentile), weight of 3600 g (90^{th} – 95^{th} percentile) and length of 52 cm (75^{th} – 90^{th} percentile). The neurological examination was normal. Laboratory investigations revealed the following: hemoglobin 21 g/dl and white blood cell count 10.000/mm^3. The blood concentrations of sugar, electrolytes, calcium, phosphorus, creatinine, total protein, albumin, ammonia, pyruvate, lactate, alkaline phosphatase, SGOT and SGPT were all within normal limits. X-rays of the chest and skull were normal as were the findings on cranial ultrasonography.

Arterial blood gases showed no evidence of acidosis or ketosis. At 12 hours of age the infant was markedly hypotonic and lethargic. He began to have apnea, hiccups and tonic-clonic seizures. Serial blood and CSF aminoacid analyses (on a LKB 4151 Alpha Plus Amino Acid Analyzer) demonstrated remarkably elevated glycine levels. The serum glycine concentration was 1949 µmol/L (normal: 104-254 µmol/L) and CSF glycine concentration was 415.5 µmol/L (normal: 5 ± 2 µmol/L). The CSF/plasma glycine ratio was 0.11 (normal: 0.02-0.03).

On the seventh day of life, a decrease in the patient's respiratory rate and apnea were noted. Assisted ventilation was initiated. Oral sodium benzoate therapy was administered along with a protein-restricted diet (1 g/kg/day). Folic acid at a dose of 2-5 mg/day was added to his therapeutic regimen. His general condition partially improved on the 25^{th} day. When spontaneous respiration began, assisted ventilation was discontinued.

Discussion

NKH is an autosomal recessive disorder of glycine metabolism which is characterized by elevation of glycine in plasma, urine and particularly in CSF[1]. Glycine levels in CSF are distinctly higher in NKH as compared with those in ketotic hyperglycinemia, and the ratios of CSF to plasma are clearly different. The high ratio in NKH does not change even when the plasma glycine level falls due to administration of sodium benzoate or to other therapeutic approaches[1,7,8].

In NKH there is a defect in the major pathway of glycine catabolism in the formation of serin from glycine. The glycine cleavage system (GCS), which converts glycine to CO_2, NH_3 and a single carbon tetrahydrofolate derivative, is composed of four protein components: P protein (a pyridoxal phosphate-dependent glycine decarboxylase), H protein (a lipoic acid containing protein), T protein (a tetrahydrofolate-requiring enzyme) and L protein (Lipoamide dehydrogenase). It has been proposed that a defect in any of these four components may lead to the development of NKH[1,3,9].

The GCS is specifically expressed in the liver, kidney and brain. Liver biopsy is, therefore, currently necessary for enzymatic diagnosis of NKH. Transformed lymphoblasts are also used for the diagnosis of NKH[10]. A large body of recent evidence suggests that enhanced activation of the N-methyl D aspartate (NMDA) type of excitatory aminoacid receptors may contribute to the pathophysiology of NKH and is important in the regulation of developmental synaptic plasticity. Evidence indicates that a high CSF concentration of glycine in NKH may contribute to the pathogenesis of this disease by overactivating NMDA receptors via an action at the associated glycine modulatory site[11,12].

The neonatal type is the most common type of NKH. Patients develop rapidly progressing neurological symptoms in the neonatal period such as muscular hypotonia, depressed Moro response, seizures (often myoclonic), apneic attacks and lethargy or coma. Most patients die within a few weeks of life, whereas the survivors show severe psychomotor retardation[4]. Our patient showed the clinical picture of the neonatal onset form of the disorder. The high CSF glycine/plasma ratio gave further evidence to the diagnosis of NKH. Luder et al.[13] described transient nonketotic hyperglycinemia in two neonates. Unlike these cases, in our case hyperglycinemia was established on the third day of life.

Various forms of treatment have been tested in NKH. Exchange transfusion or peritoneal dialysis may be life-saving in the neonatal period, but its effect is only temporary[9]. The plasma glycine concentration may be lowered by the restriction of protein intake and by the administration of sodium benzoate. We gave a protein-restricted diet with sodium benzoate to our patient, which was partially effective in the control of symptoms. Recently, the NMDA receptor antagonist, ketamin, was administered to a patient with hNKH, and improvement in hyperirritability, voluntary movement and electroencephalographic findings was noted[11]. These therapeutic approaches are merely supportive and may lower the blood glycine level but not that of CSF. It can be said that they have no effect on the outcome of this metabolic disorder.

Prenatal diagnosis of NKH has become possible in recent years. Thus the diagnosis of NKH should be considered in markedly hypotonic newborns in

order to give genetic counselling to the parents and offer them a prenatal diagnosis in subsequent pregnancies[14].

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