Nonketotic Hyperglycinemia in a Neonate

Vineet Sehgal
S. Ramji

Hyperglycinemia represents a group of disorders characterized by elevated concentrations of glycine in body fluids. Two types exist, the ketotic and non-ketotic. In the ketotic type, the most striking feature is ketoacidosis, which begins early in life and in which hyperglycinemia is secondarily associated with organic acidemias. Nonketotic hyperglycinemia (NKH) is a disorder of glycine metabolism due to a molecular defect in the glycine cleavage system (GCS)(1,2). Though NKH is a well-documented entity, to the best of our knowledge there are no reports of this disorder from India, the result of inadequate diagnostic facilities. We report a case of NKH in a neonate, with a review of its recent therapeutics.

Case Report

A male baby weighing 2490 g was born at term, after an uneventful antenatal period, to a 25-year-old fifth gravida mother. He was the product of a non-consanguineous marriage. There was history of early neonatal deaths of previous 3 male term infants. They had no history of birth asphyxia and followed an identical course of lethargy and floppiness soon after birth, with inability to suck on the breast, followed by seizures, progressive sensorial deterioration and death. One female sibling, 8 years old, is alive and apparently healthy.

This neonate presented at 11 hours of age with lethargy, weak cry and inability to feed. On examination the baby was normothermic, pink with a heart rate of 136/min, respiratory rate of 48/min and normal peripheral perfusion. There were no gross congenital anomalies. The sensorium was depressed with minimal spontaneous eye opening and limb movements. Response to painful stimuli was decreased. Neonatal reflexes were sluggish. There were no focal neurological deficits. In view of the clinical presentation and similar history in earlier siblings, possibility of an inborn error of metabolism was kept and the baby accordingly investigated.

Hematological investigations revealed:

- TLC 8400 /cumm (polymorphonuclears 70%, lymphocytes 30%, immature to total neutrophil ratio 0.07) and (µESR 1 mm fall in 1st hour. Initial and subsequent blood sugars ranged between 45 to 90 mg/dl.
- Arterial blood gas analysis yielded pH 7.34, bicarbonate 18.2 mmol/L, base excess 3.4 mmol/L, paO₂ 90 mmHg, and paCO₂ 32 mmHg. Blood ammonia was 56 (µg/dl (normal : 90-150 mg/dl) and serum creatinine 0.5 mg/dl. Ultrasound of cranium was within normal limits.

The baby was initially started on expressed breastmilk by nasogastric tube, which he tolerated well. By 36 hours of life, the baby’s sensorium was completely obtunded and respiration became shallow. At this juncture, enteral feeding was discontinued and the child provided intravenous fluids and oxygen by hood. At 70 hours of age, the baby had recurrent myoclonic seizures, which did not respond
to phenobarbitone and phenytoin. At this stage, the baby was provided assisted mechanical ventilation. Inspite of adequate supportive management, the baby died on the fifth day of life.

The results of gas chromatographic-mass spectroscopy analysis of urine and blood for organic and aminoacids revealed markedly elevated levels of glycine. Glycine levels in blood were 8.2 mg/dl (normal : 3.1 ± 0.8 mg/dl) and in urine 18.4 umol/mg creatinine (normal : 2.3 ± 1.4 umol/mg creatinine). The other organic and aminoacids were within normal limits.

Discussion

NKH is a relatively frequent metabolic cause of overwhelming illness in infancy(1). Over 150 cases have been reported(2). The exact prevalence is not known, though it is estimated to be 1 in 250,000. It is common in northern Finland, where the prevalence is 1 in 12,000 (1) and is transmitted as an autosomal recessive trait. In the present family, only the male children manifested clinically, suggesting that a sex-linked mode of inheritance may also exist.

NKH classically presents as a life threatening metabolic encephalopathy in the neonatal period. Most infants appear normal at birth and remain asymptomatic for a brief period, seldom longer than 48 hours(2). They present with rapidly progressive neurological symptoms such as lethargy, poor feeding, seizures, high pitched cry and generalized hypotonia. Hiccups are frequently observed. Most patients lapse into coma and die within a few weeks. Survivors usually have severe psychomotor retardation, spasticity, microcephaly and uncontrolled seizures(1,2). The present case had a clinical presentation consistent with the classical type of NKH and the history in the earlier siblings also suggests that they too probably had the same disorder. During the first few weeks of life, a characteristic electroencephalogram (EEG) pattern is seen with bursts of large amplitude sharp waves, arising periodically from a hypoactive background. The so called burst-suppression pattern changes by the end of the first month to hypsarrhythmia(1,2). Cortical atrophy and delayed or deficient myelination may be seen on CT or MRI scan(4).

The late onset or infantile type of NKH has a variable onset from "infancy to adolescence, the patient usually remaining asymptomatic in the neonatal period(2). The presentations include seizures, delayed development or mental retardation, spinocerebellar degeneration and optic atrophy(5,6). Transient NKH is also reported, which has a variable prognosis(7).

Diagnosis is based on the findings of hyperglycinemia and hyperglycinuria in the absence of an organic acid disorder. Absence of ketoacidosis and exclusion of organic acidemias is crucial. During the investigation of neonatal seizures due to a suspected inborn error of metabolism, absence of common biochemical abnormalities evaluated (hyperammonemia, lactic acidosis, ketoacidosis) should suggest the possibility of classical NKH. Glycine levels in cerebrospinal fluid (CSF) are also elevated, the ratio of CSF and plasma glycine characteristically being greater than 0.09, whereas under normal circumstances and in ketotic hyperglycinemia, it is below 0.04(1,2). CSF examination was not done in the present case as neither an infective condition nor this specific metabolic disorder was suspected at presentation. Liver biopsy can be performed for the enzymatic diagnosis of NKH, as GCS is expressed in the liver(3). GCS is also induced in B lymphocytes in the peripheral blood by Epstein Barr virus (EBV) and enzymatic assay can be performed. This method is useful for
differentiating NKH from ketotic hyperglycinemia and for detection of carriers(8). Prenatal diagnosis is possible by chorionic villus sampling to estimate GCS activity between 8th-12th week of gestation(9).

The pathophysiologic effects of hyperglycinemia are attributed to the inhibitory property of glycine at post synaptic strychnine sensitive receptors particularly in the spinal cord and brain stem, and over stimulation of the excitatory gluta-minergic N-Methyl-D-aspartate (NMDA) receptors, particularly in the forebrain(10). Measures to lower the glycine concentration in NKH patients have included protein restriction, synthetic diet devoid of glycine and it's precursor serine, promotion of renal excretion by benzoate, administration of ursodeoxycholic acid, strychnine and benzodiazepines. The response has generally remained unsatisfactory(1,2).

Recently, NMDA receptor antagonists have been used with modest success. Oral administration of ketamine (8 mg/kg/day, in four divided doses)(11), tryptophan (100-150 mg/kg/day)(12) and dextromethorphan (5-35 mg/kg/day in three to four divided gradually increased doses) in combination with benzoate (500-750 mg/kg/day)(10,13) have brought about a partial improvement of neurological symptoms and EEG findings. Though aggressive management employing assisted ventilation, exchange transfusions and peritoneal dialysis along with the aforementioned therapeutic approaches has decreased the mortality, the long term morbidity due to NKH has remained unacceptably poor.

Acknowledgment

We wish to acknowledge Sapporo City Institute of Public Health, Japan for carrying out the GC-MS analysis for organic and amino-acids.

REFERENCES


