Nonketotic Hyperglycinemia in a Neonate

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Abstract

Nonketotic Hyperglycinemia (NKH) is an autosomal recessive disorder characterized by rapidly progressing neurological symptoms such as muscular hypotonic seizures, apnea attacks, lethargy and coma, mostly in the neonatal period. Most patients die within a few weeks whereas the survivors show psychomotor retardation. Increased glycine concentrations in plasma, urine and cerebrospinal fluid (CSF) are biochemical features of this disorder. The ratio of CSF to plasma >0.09 is diagnostic. The primary defect is in the glycine cleavage system (GCS). No specific treatment is available. Prenatal diagnosis is feasible by determining the activity of GCS in the chorionic villi. We report a full term female baby born to primigravida mother by normal vaginal delivery. She developed seizures and other complications and received intensive management and recovered. At the age of thirty two days the baby was discharged in good condition and advised follow up. Unfortunately, the baby did not come for follow up.

Keywords: Nonketotic hyperglycinemia, NKH in neonate.

Case

A full term female baby was born to a primigravida mother after normal spontaneous vaginal delivery. Her Apgar score was 7 and 9 at 1 and 5 minutes respectively. Growth parameters were: weight 1.7 kilogram, head circumference 32 centimeters and length 43 centimeters. She was small for gestational age. The blood chemistry including blood sugar and serum calcium were normal. Parents of the patient are first degree cousins. After four hours oral feeding was started. The level of consciousness of the baby started deteriorating and needed mechanical ventilation. Sepsis and inborn error of metabolism was suspected and the patient was put on antibiotics (Injection Ampicillin and Gentamycin) and intravenous fluids. Feeding was stopped. Blood culture yielded no growth. Tandem spectrometry of blood and cerebrospinal fluid (CSF) revealed high CSF glycine (780um). The CSF/blood glycine value was abnormal (0.66) while normal level <0.04; so her condition was consistent with non ketotic Hyperglycinemia. Blood amino acid showed elevated glycine at 1180um (cut off is 1000um). Ultrasonography of brain revealed agenesis of corpus callosum with dilated lateral ventricles. No other brain malformation was found.

Nasogastric tube feeding was started on day 6th and was gradually increased to full feed. In the second week patient developed skin mottling, peripheral cyanosis, and desaturation. Ventilatory setting was increased. Sepsis was suspected and antibiotics were changed to Injection Vancomycin and Tienam. X ray chest revealed pneumonia. Septic screening yielded Klebsiella pneumoniae from tracheal aspirate and also from urine culture. The level of consciousness started to improve at the age of two weeks. Patient was kept on minimal ventilatory setting and gradually extubated. Her blood chemistry including serum electrolytes, blood gases, serum ammonia and routine urine analysis were normal. CT scan brain revealed dilatation of ventricular system mainly affecting lateral and third ventricles and low density of the periventricular white matter of both cerebral hemispheres suggestive of periventricular leukomalacia. Agenesis of the corpus callosum was not clearly defined. Electroencephalography (EEG) recording showed suppression burst pattern of cerebral discharges with multifocal high voltage sharp waves as well as multispike slow wave discharge consistent with non ketotic Hyperglycinemia.
Hospital course
There was rapid deterioration in the clinical condition of the patient including seizures within four hours after birth. Seizures were controlled with in two days with Injection of Phenobarbitone. Patient developed generalized hypotonia, loss of consciousness and needed mechanical ventilatory support for three weeks. Patient developed pneumonia and urinary tract infection and was treated with appropriate antibiotics. Nasogastric tube feeding was gradually started in the first week with soya milk till full feed. Patient started showing improvement at the age of third week. Levels of consciousness, tone and body movements were regained to normal. At the end of third week, patient was accidentally extubated and was put under oxyhood and showed marked clinical improvement. Movements were active & normal. Vital signs were normal. Tube feeding was replaced by demand feeding gradually. At the age of thirty two days the baby was discharged in good condition and advised to come for follow up. Unfortunately, baby did not come for follow up.

DISCUSSION:
In NKH patient’s clinical manifestations develop in the first few days of life, generally hours to 8 days after birth. They develop lethargy, hypotonia and poor sucking and progress to apnea, hiccough, myoclonic seizures and coma. They often require assisted ventilation and most of them die in the neonatal period. Survivors develop intractable seizures and mental retardation. In our case the baby started convulsing immediately after birth. Four forms of NKH have been identified: neonatal, infantile, late onset and transient. Neonatal is the commonest type. Most affected infants appear normal at birth except for patients who present prenatally with in utero brain damage like dysgenesis of the corpus callosum and gyral malformations. After a short interval (seldom longer than 48 hours), the patient develops rapidly progressing neurological symptoms such as muscular hypotonia, depressed Moro response, seizures, apneic attacks and lethargy or coma. Most patients die within a few weeks. Hoover-Fong et al observed in 65 patients (36 boys, 29 girls) collected from 58 families. One-third of the subjects died.

Two-thirds of infants were ventilated during the neonatal period; of these, 40% died. Ninety percent had confirmed seizures, 75% during the first month of life. An abnormal corpus callosum and/or hydrocephalus were associated with especially poor gross motor and speech development. Twenty five patients showed severe psychomotor retardation. Convulsive seizures range from myoclonic to grand mal convulsions. Hiccupping is often seen during the first few week of life. A characteristic electroencephalogram (EEG) pattern with bursts of high complex waves of 1-3 S arising periodically from a hypoactive background is seen. This so called burst suppression pattern is present immediately after birth, preceding clinical symptoms. It disappears at the end of the first month and changes to hypsarrhythmia. Muscular hypotonia is prominent during the neonatal period but thereafter spasticity develops gradually. Hyperglycinemia represents a group of disorders characterized by elevated concentrations of glycine in the body fluids. There are two types of hyperglycinemia: the nonketotic type and the ketotic type. Nonketotic Hyperglycinemia (NKH) is a disorder of glycine degradation due to a primary defect in the glycine cleavage system (GCS). The genetic backgrounds of the neonatal and infantile types have been largely clarified by a comprehensive mutational screening of genes encoding three components of the GCS, while the molecular pathogenesis of the late-onset and transient types are largely unknown. In the central nervous system of vertebrates, the GCS has been identified in astrocytes and neural stem cells. The GCS in astrocytes is co-localized with N-methyl-D-aspartate receptors, and is thought to maintain the glycine level around the receptors, while the physiological and pathological roles of the GCS in neural stem
cells remains to be elucidated. There is moderate to severe hyperglycinemia (as high as eight times normal) in blood. Elevation of glycine concentration in the spinal fluid (15-30 times than normal) and the high ratio of glycine concentration in spinal fluid to that in plasma (a value greater than 0.09) are diagnostic of NKH. Serum PH is normal; plasma serine levels are usually low. About 30% of affected infants die despite supportive therapy.

Those who survive develop profound psychomotor retardation and intractable seizure disorder. Reported autopsies of these cases reveal cortical atrophy, white matter degeneration, thin corpus callosum, and cerebellar atrophy, with variable degrees of gliosis. NKH is inherited as an autosomal recessive trait. NKH is a rare inborn error of glycine metabolism with an incidence of 1 in 200,000. The disease is more common in Finland (1:12,000) and in the Israeli-Arab population. In one study from India it was found to be the fourth most common inborn error of amino acid metabolism. The gene for P protein is located on the short arm of chromosome 9. The gene for H and T proteins are mapped to the long arm of chromosome 3. NKH can produce central nervous system anomalies like agenesis of the corpus callosum. No effective treatment is available. Based on the hypothesis of NMDA receptors activation by glycine, glycine decreasing agents i.e., sodium benzoate and NMDA antagonists ketamine and dextromethorphan have been tried. The outcome is usually poor, though occasional satisfactory results have been reported.

In conclusion the awareness of treating physician about NKH may help to identify such cases. The use of tandem spectrometry will help to identify more such cases.

REFERENCES:

Conflict of Interest: None
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