Opsoclonus in a Neonate with Nonketotic Hyperglycinemia

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Citation

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Abstract

Nonketotic hyperglycinemia (NKG) is a non-acidotic, non-hyperammonemic inborn error of metabolism presenting in the neonatal period. Often babies with NKG present in the first week of life with altered sensorium, seizures, apnea and respiratory failure (1, 2). Definite diagnosis is possible with CSF to glycine ratio and estimation of glycine cleaving enzyme levels in the liver. Here we report Opsoclonus in a baby with NKG.

CASE

Baby H, a male infant, was admitted for observation in view of a family history of two previous neonatal deaths. The infant was born at term by a normal vaginal delivery, following an uncomplicated pregnancy to a 25 year old woman,. It was a product of 3rd degree consanguineous marriage. He was normal at birth with good Apgar scores but the cry was weak. The parents noted that the activity and cry of this baby was similar to the previous siblings who had died on their seventh and sixth days of life respectively.

The baby's weight, length and OFC at birth were 3010grams, 52cms and 34cms respectively. Except for the weak cry, the rest of the neurological examination was normal. Feeds were started orally along with glucose monitoring. On the second day, Baby H became dull, hypotonic with an absent cry and occasional hiccups. A metabolic and sepsis screen was sent and Baby H was started on Intravenous (IV) fluids. On day three, spontaneous activity decreased, multi-focal clonic seizures and poor respiratory effort were noted. Sepsis screen was negative, blood sugar, serum electrolytes, ammonia, liver function tests, urea, creatinine and neurosonogram were normal. Serum aminoacidogram, urine organic acids and CSF glycine levels were sent. The infant was started on mechanical ventilation along with folate, carnitine, dextromethorphan and sodium benzoate. Seizures were controlled with IV Phenobarbitone. Serum aminoacidogram revealed elevated glycine levels 1034umol/L (ref 180-311umol/l) and CSF glycine was 113.74 umol/l (ref 5-10 umol/l). CSF to serum glycine ratio was 0.11. On the fourth day and subsequently the baby was noted to have peculiar eye movements (video). On opening the eyelids, there was an irregular, to and fro conjugate inward movement of both eyes (opsoclonus). These movements were not associated with any other abnormal limb movements or with heart rate variability. The frequency of eye movements was maximum on opening the eyelids. The parents requested for withdrawal of ventilatory support and baby died on the sixth day of life. MRI head, EEG and GCS could not be done.

DISCUSSION

Nonketotic hyperglycinemia is a rare autosomal recessive inherited inborn error of metabolism. The metabolic defect of NKH is in the glycine cleavage system (GCS), an enzyme system with four components: the P, the H, the T, and the L protein ($_3$). The four variants of NKH are neonatal, infantile, late onset and transient based on its clinical course; most patients with the neonatal type have a defect in the P protein. Due to deficient activity of the GCS, the major pathway for the catabolism of glycine, large quantities of glycine accumulate in all body tissues. High concentrations of glycine in the central nervous system produce excito-neurotoxicity, seizures and brain damage (more specific?), through the over stimulation of the N-methyl-D aspartic acid (NMDA) receptor, via an action at the associated glycine modulatory site($_3$).

After a period of well being in the first 1 or 2 days of life, most neonates with NKG present with poor feeding, altered sensorium, seizures, hypotonia, apnea and respiratory failure, Hiccups occur because of diaphragmatic spasms. Some surviving neonates develop intractable seizures and mental retardation. Opsoclonus as present in our case has not been reported previously. Similar to hiccups, these eye movements might occur due to the spasm of the ocular

muscles. Opsoclonus might become an important clinical finding if found in subsequent reports.

Classically NKG is a non-ketotic, non-hyperammonemic inborn error of metabolism. The main diagnostic feature is elevation of glycine in serum, urine and CSF. A CSF to serum glycine ratio greater than 0.08 is diagnostic. The serum and CSF glycine levels in our patient were diagnostic for NKH. Liver GCS activity is indicated to determine the severity of the disease and for prenatal diagnosis. Carnitine deficiency ([4]) and transient hyperammoniemia have been reported in some cases ([5]).

NKG does not have any effective treatment. Sodium benzoates for decreasing glycine levels and dextramethorphan (NMDA receptor antagonist) have been tried in some patients for control of seizures and for clinical improvement ([6,7]). In our patient these medications along with phenobarbitone controlled the seizures but did not improve the clinical situation. Other anticonvulsants which can be used for control of seizures in these patients include diazepam-a competitor for glycine receptors, or felbamate ([6]).

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