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NONKETOTIC HYPERGLYCINEMIA*
A Report of Three Cases

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Nonketotic hyperglycinemia (NKH) is an inborn error of metabolism resulting from a defect in the formation of serine from glycine. It is characterized clinically by rapidly progressing neurological symptoms such as intractable seizures of the myoclonic or grand mal type, muscular hypotonia, lethargy, respiratory distress and persistent hiccup beginning in the first few weeks of life[1-6]. Patients who survive the neonatal period develop severe psychomotor retardation and intractable seizures[5,7-10]. Biochemical findings include high glycine concentrations in blood, urine and cerebrospinal fluid (CSF) without any organic acid accumulation[1-6].

We present the clinical and laboratory findings of three cases with NKH. To the best of our knowledge, these are the first documented cases reported from Turkey.

Case Reports

Case 1

A one-day-old girl was referred to Hacettepe University Children's Hospital because of poor activity and a previous history of sibling deaths. She was born to a gravida 4, para 4, abortion 0 healthy mother and was a product of a nonconsanguineous marriage. Pregnancy and delivery were uneventful. One female and one male sibling aged four and three days, respectively, died as a result of extreme hypotonia and feeding difficulties. Another male sibling had

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experienced intractable seizures after one month of age and died at 21 months of life.

The patient on admission, weighed 3600 g (at the 90th percentile), measured 51 cm in length (at the 75th percentile) and 37 cm in head cicumference (above the 95th percentile). She was extremely hypotonic with irregular respiration complicated by frequent hiccups.

Laboratory investigations revealed the following: hemoglobin 21.75 g/dl and White Blood Cell count 4000/mm^3. Glycine was found to be increased in the serum (0.87 μM/ml, normal[11] 0.209 ± 0.046 μM/ml) and CSF samples (0.10 μM/ml, normal[11] 0.005 ± 0.002 μM/ml). An EEG demonstrated severe abnormality of bioelectric activity. No organic acid was detected both in the serum and urine of the patient by Gas Chromatography-Mass Spectrometry (GC-MS).

A diagnosis of NKH was made and oral sodium benzoate therapy was initiated along with a protein restricted diet. Her general condition improved and she was discharged on the 20th day. Frequent jerking movements were noted when seen at one month of age. Diazepam (1 to 3 mg/kg/day in six divided doses) and folic acid (2.5 mg/day) were added to her therapeutic regimen. Seizures decreased in frequency but could not fully be controlled. She showed progressive neurologic deterioration. While receiving diazepam, she showed a lack of interest in environmental stimuli and therefore its dose was tapered and replaced with strychnine (0.3 mg/kg/day). Since seizures increased in intensity and frequency, the use of diazepam in treating the patient became necessary. Seizures ceased when diazepam therapy was resumed. The patient showed no further improvement and died at two years of age.

Case 2

A six-month-old girl was brought to Hacettepe University Children's Hospital because of convulsions, irritability and respiratory difficulties. The convulsions had started 20 days prior to her admission. Her parents were first cousins. Four male siblings had died at ages ranging from 5.5 to 14 months of convulsions and vomiting.

The patient on admission showed abnormal physical findings including marked hypotonia and respiratory failure. She weighed 5.6 kg (below the 5th percentile), was 62.5 cm in length (at the 10th percentile) and her head circumference was 41.5 cm (at the 25th percentile).

Laboratory data included hemoglobin 12 g/dl and White Blood Cell count 9400/mm^3. The blood concentrations of sugar, electrolytes, calcium, phosphorus, creatinine, total protein, albumin, ammonia and activities of alkaline phosphatase, SGOT and SGPT were all within normal limits. Spinal tap and electromyography

showed normal findings. Glycine concentrations in plasma and CSF were 1.05 μM/ml and 0.22 μM/ml, respectively.

On the basis of these findings, NKH was suspected. Intravenous fluid and electrolyte were administered. A decrease in respiratory rate and apnea were noted. Assisted ventilation was started. The patient died of cardiorespiratory arrest on the second day of admission.

Case 3

A five-month-old boy was referred to Hacettepe University Children's Hospital with the chief complaint of convulsions which had begun at 40 days of age. He experienced 10-12 convulsive attacks of 1-2 minutes duration on each following day. He was the first child of an uncomplicated full-term pregnancy and of a marriage between two first cousins.

Neurologic examination revealed that the infant showed no interest in his environment. He was unable to recognize his mother and control his head. He weighed 6 kg (at the 10th percentile), measured 68 cm in length (at the 25th percentile) and 41 cm in head circumference (at the 25th percentile).

Laboratory investigations included normal serum levels of lactate, pyruvate and ammonia. Computed tomographic brain scan showed partial agenesis of the anterior part of the corpus callosum. Increased concentrations of glycine both in plasma (0.46 μM/ml) and in CSF (0.06 μM/ml) led us to the diagnosis of NKH.

Discussion

NKH is an autosomal recessive disorder of glycine metabolism in which there is a defect in the major pathway of glycine catabolism of the formation of serine from glycine (Fig. 1). The glycine cleavage system 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 (a lipoamide dehydrogenase)[3,5,6,12,13]. It has been proposed that a defect in any of these four components may lead to the development of NKH. Although, NKH cases due to a defect in either P-protein, H-protein or T-protein have been reported in the literature, the exact biochemical nature of the disorder is still obscure. Threonine dehydratase deficiency has also been suggested as a primary lesion of NKH based on undetectable levels of this enzyme in liver specimens obtained at autopsy[14]. The possibility of ketotic hyperglycinemia which appears to be secondary to propionic acidemia and methylmalonic aciduria must be excluded in cases with hyperglycinemia and glycinuria by appropriate laboratory techniques. NKH differs from the ketotic one in that there is no ketosis and organic acid accumulation in NKH. In none of the cases presented were organic acids detected by GC-MS.

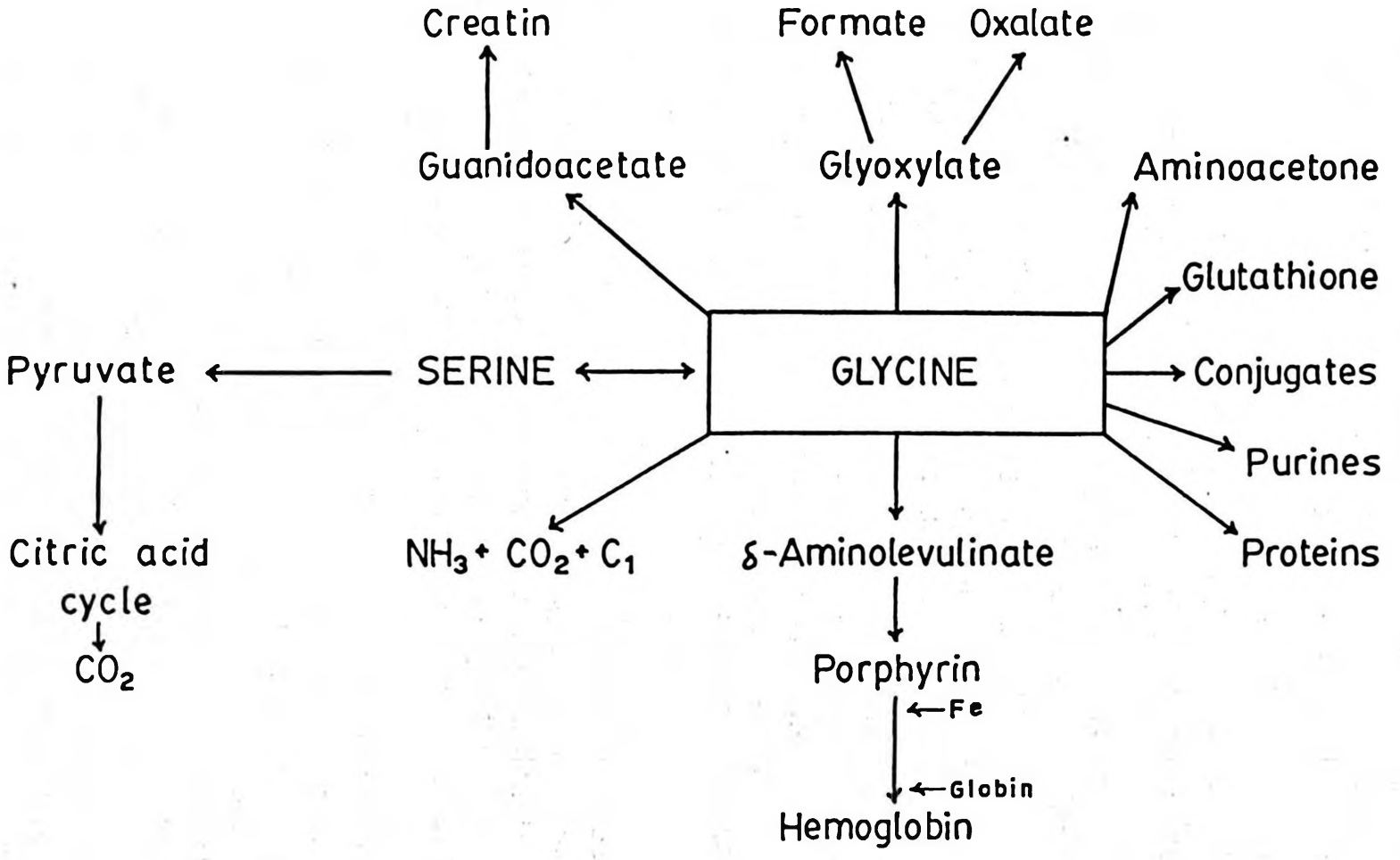

Fig. 1: Pathways in glycine catabolism.

Patients affected by NKH usually present with lethargy, muscular hypotonia, respiratory distress and convulsions in the neonatal period and die within a few weeks or months[1-6]. There have been cases, however, diagnosed as having NKH and in a search for an etiology regarding their mental-motor retardation later in their lives it was indicated that the disorder is genetically heterogenous[5,8,12,13]. Among the cases reported here, Case 1 showed the clinical picture of the neonatal onset form of the disorder although the biochemical findings were not so severe. Case 3 may be considered as mildly affected by the disorder. Case 2 had developed normally for the first few months of life and then had a rapid degenerative course leading to death similar to the case reported by Trauner et al[8].

In NKH, large amounts of glycine accumulate in plasma, urine, CSF and brain tissue without increase of organic acids[1-6]. An overload of glycine which has an inhibitory neurotransmitter activity, causes postsynaptic inhibition and then demyelination by altering the normal balance of amino acids available for protein synthesis in the developing brain, and may be responsible for the observed neurological symptoms in patients with NKH[8]. The rise of glycine in CSF seems to be typical of NKH and the ratio of the CSF concentration of glycine to that of the plasma is remarkably higher in patients with NKH than in hyperglycinemic patients with organic aciduria[1-6]. The high CSF glycine/plasma glycine ratio in Case 2 and the mildly elevated ratio in Cases 1 and 2 gave further evidence in the established diagnosis of NKH. Cases 1 and 3 with severe clinical expression in whom the ratio was abnormal, but less elevated than in the classical form (0.17 ± 0.09), as in Case 2, characterized heterogeneity of expression (Table I). The administration of ^{13}C-glycine to patients with NKH and the consecutive measurement of the $^{13}CO_2/^{12}CO_2$ ratio in expired air, a noninvasive method described by Brockstedt et al[15], allows clinicians to make a distinction between the different types of NKH. This method could not be applied in our cases.

Various forms of treatment have been tested in NKH, either separately or in combination. Exchange transfusion or peritoneal dialysis may be lifesaving in the neonatal period but its effect is only temporary[5,16]. The plasma glycine concentration may be lowered by the restriction of protein intake and by the administration of sodium bezoate[2,5,17]. We gave a protein restricted diet to all our cases, except Case 2, who died when the diagnosis was made. Strychnine has been used in the treatment of NKH. As a postsynaptic glycine antagonist, strychnine competes with glycine for receptor sites on the postsynaptic membrane[18,19]. Diazepam, another competitor for glycine receptors, is also used in high doses in patients with NKH in combination with choline and folic acid to facilitate the single carbon unit transfer reactions that may be impaired in NKH[20]. We tried the latter therapeutic regimen on Case 1 and found it to be more effective in the control of the patient's symptoms.

TABLE I: Findings in Three Patients with Nonketotic Hyperglycinemia (NKH)

	Case 1	Case 2	Case 3
Onset of symptoms	1st day of life	6 months of age	40th day of life
Initial signs/symptoms	Hypotonia	Convulsion Hypotonia	Convulsion Hypotonia
Diagnosis of NKH made	On the 1st day of life	At age 6 months	At age 5 months
Glycine levels at time of diagnosis			
Plasma (± µM/ml)	0.87	1.05	0.46
CSF (± µM/ml)	0.10	0.22	0.06
CSF/Plasma glycine ratio*	0.11	0.20	0.13
Treatment	Protein restricted diet, sodium benzoate, diazepam, folate	–	Protein restricted diet, sodium benzoate
Outcome	Died at 2 years of age	Died on the 2nd day of admission	Lost to follow-up at 8 months

* Normal CSF/Plasma glycine ratio: 0.02-0.03

Although limited, our experience with the three cases of NKH supported the conclusion that all these therapeutic approaches are only supportive and may lower the blood glycine level but not that of CSF. Therefore, it can be said that they have no effect on the outcome of this metabolic disorder.

The cases presented here and those reported in the literature indicate that there is need for further research regarding the documentation of the glycine cleavage enzyme system and new pharmacologic approaches for a sustained and more effective therapy.

Summary

Nonketotic hyperglycinemia (NKH) is an inherited disorder of glycine metabolism. It usually presents with hypotonia, generalized myoclonic seizures, respiratory distress and hiccup in the neonatal period, and is characterized clinically by

elevated concentrations of glycine in plasma, spinal fluid and urine. The elevation of CSF glycine and the absence of ketoacidosis are the useful tools in distinguishing NKH from other hyperglycinemic states.

In this report, the clinical and laboratory findings of three cases with NKH are presented. According to the data obtained from these cases and from the literature, it is obvious that our current state of knowledge of this disorder is incomplete. Therefore, a sustained and effective therapy awaits further research on the etiology of NKH and the use of new pharmacologic agents.

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