Genetics Newborn Screening Program
Health Professional Fact Sheet

Nonketotic Hyperglycinemia (NKH) also known as Glycine Encephalopathy

Introduction

Nonketotic hyperglycinemia (NKH) is an autosomal recessive inborn error of glycine degradation in which large quantities of glycine accumulate in all body tissues, including the central nervous system. The defect is in the glycine cleavage enzyme complex (GCS) which catalyzes the major reaction of glycine degradation and is composed of four proteins (P-, H-, T-, and L-Protein) encoded on four different chromosomes. Defects in the P, H, and T proteins have been identified in NKH. Over 80 percent of patients with the neonatal phenotype have a defect in the P-protein. Later onset cases are more likely to have defects in the H- or T-proteins. Although glycine plays many roles in intermediary metabolism, the symptoms of NKH seem to relate to glycine's function as a neurotransmitter.

Clinical Features

Neonatal form: Most patients have the neonatal phenotype, presenting in the first few days of life with lethargy, hypotonia, and refusal to feed. Wandering eye movements and intermittent ophthalmoplegia are frequent. Most patients have normal to increased deep-tendon reflexes. As the encephalopathy progresses to coma, the infants develop frequent segmental myoclonic jerks, apneic episodes, and hiccups. Even with respiratory support, approximately 30 percent of patients die in the neonatal period. Those who regain spontaneous respiration develop intractable seizures and profound mental retardation.

Routine laboratory studies of children with NKH are remarkably normal, given the severe neurologic abnormalities. The only consistent abnormality is elevation of glycine concentrations in urine, plasma, and cerebrospinal fluid. Plasma glycine concentrations in NKH range from high normal to values eight times the normal mean and four times the upper limit of normal. Urine glycine concentrations are usually elevated, but interpretation is difficult because of the physiologic hyperglycinuria that is characteristic of the newborn infant.

Patients with neonatal NKH may experience *in utero* brain damage and mothers of infants with NKH frequently report abnormal fetal movements , which are interpreted as persistent *in utero hiccups*.

Infantile form: Patients present with seizures and have various degrees of mental retardation after a symptom-free interval and seemingly normal development for up to six months.

Mild-episodic form: Patients present in childhood with mild mental retardation and episodes of delirium, chorea, and vertical gaze palsy during febrile illness.

Late onset form: Patients present in childhood with progressive spastic diplegia and optic atrophy, but intellectual function is preserved and seizures have not been reported.

Diagnosis

Newborn screening—Tandem mass spectrometry—Glycine

Confirmation—a second sample may be requested or follow up testing will be done at a Metabolic Treatment Center.

Several disorders are associated with hyperglycinemia and/or hyperglycinuria. It is critical to establish the correct diagnosis, as therapy and prognosis are dramatically different. Propionic acidemia, methylmalonic acidemia isovaleric acidemia, and β-ketothiolase deficiency can have similar

presentations. However, CSF and brain glycine content are normal in these disorders, which distinguishes them from NKH.

Treatment

No effective treatment exists, but several experimental therapies directed at decreasing the glycine concentration are under investigation.

Many therapeutic strategies have been tried in an effort to ameliorate the intractable seizures and relentless brain damage characteristic of this disorder, but none of these approaches has been consistently effective. Reduction of tissue glycine levels by administration of glycine-free or glycine-serine-free diets resulted in reduced plasma and urine glycine concentrations but had no effect on seizure frequency or developmental progress. Sodium Benzoate, which conjugates with glycine to form hippurate, which is excreted in the urine, has been used extensively to reduce glycine in the blood and cerebrospinal fluid. It is also an anticonvulsant and is used to treat the seizures. Dextromethorphan has been found, in some cases, to prevent or reduce seizures and death and to prevent the death of brain cells. But dextromethorphan can have side effects such as irritability, involuntary movements, refusal to eat, troubled sleeping and breathing suppression. The side effects do vary from child to child and is thought to relate to an individual's ability to process this drug. Another method of reducing the concentrations of glycine from the blood is by dialysis or an exchange transfusion. It is also important for the primary care provider and the Metabolic Treatment Center to develop an on-going collaborative relationship in caring for these patients.

Patients surviving the neonatal period, while at risk of death from sudden onset of intractable seizures, are not certain of it. It is essential that patients receive appropriate medical care, including nutritional support, anticonvulsant therapy, and developmental interventions, such as occupational, physical, and speech therapies.