A Treatment of Non-ketotic Hyperglycinaemia

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The treatment comprising a special diet (without glycine, serine, and with a reduced amount of threonine), strychnine nitrate and ursodesoxycholic acid (UDCA) led to normoglycinaemia in this form of severe non-ketotic glycine encephalopathy. Diet and treatment were well tolerated but without significant effect upon psychomotor development. This treatment should be more effective if administered before irreversible brain damage occurs, particularly in moderate and chronic forms of NKH.

In a 4-month-old child with familial NKH presenting as severe encephalopathy, three therapeutic measures were tried, separately or together, during a 7 month period: (a) special semisynthetic diet without glycine and serine, and with a reduced amount of threonine; (b) strychnine nitrate; (c) ursodesoxycholic acid (UDCA). Serum glycine, taurine and bile acid levels were measured regularly, as well as urinary glycine. Glycinaemia was maintained below 500 μmol/l level only during the period of combined treatment.

HYPOTHESIS

Non-ketotic hyperglycinaemia (NKH, McKusick 23830) is presumably due to a primary defect in the glycine cleavage system (Tada et al., 1969), characterized by high glycine concentrations in blood, urine and cerebrospinal fluid (CSF), without accumulation of organic acids (Carson, 1982). The rise of glycine in CSF seems specific to NKH and may be related to the observed neurological symptoms (Krieger and Nigro, 1983).

Various forms of treatment have been tested, separately or together: exchange transfusion or peritoneal dialysis during acute episodes; low protein diet, sometimes with added methionine; semisynthetic low glycine/serine diet; α-methylserine; sodium benzoate; choline; folic acid; N5-formyltetrahydrofolate; strychnine; diazepam (Mendelson, 1982). However, the clinical improvement was very limited in the "classic" early-onset, severe form of NKH.

It is well known that bile acids conjugate with glycine. Thus we have suggested that UDCA could decrease glycinaemia. In order to further investigate this hypothesis, we have repeatedly examined, under various conditions, glycinaemia and glycine excretion in our NKH patient, in the absence or the presence of UDCA.

CASE REPORT

The index case, a girl of Turkish origin, was born after an uneventful pregnancy. She rapidly presented neonatal distress with myoclonic seizures. A diagnosis of Steinert disease was suspected, but subsequently invalidated by e.m.g. of mother and child and by muscle biopsy.

At 10 weeks, the hypotrophic infant was admitted in our paediatric department for hypsarrhythmia which yielded to ACTH treatment. The e.e.g., initially totally disorganized, became more stable: the fundamental rhythm was replaced by low monomorphous waves, with or without few paroxystic activities. CAT scan of the brain was normal. Psychomotor development, however, was lacking.

A high level of glycine in urine and blood, as well as in CSF, confirmed the diagnosis of NKH. The other amino acids were in the normal range and abnormal organic aciduria was generally absent.

The girl is now 2 years old; in spite of the therapeutic attempts (see below), her neurological condition remains poor.

FAMILY HISTORY

Three other siblings died soon after birth; all of them were full-term infants, normal at birth, but soon developed severe encephalopathy. Two girls died, aged 5 days, in Turkey, apparently without any diagnosis. A boy, born in our department, was diagnosed as NKH on the 5th day (blood glycine 960 μmol/l, CSF glycine

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390 μmol l

This boy died on the 19th day. The similar clinical features and outcome suggest, for the three infants, the diagnosis of NKH.

Two brothers are healthy.

**THERAPEUTIC ATTEMPTS**

Three therapeutic methods were used in our NKH patient between the ages of 4 and 11 months:

(a) strychnine nitrate (0.25 mg kg

(b) a semisynthetic diet providing, per kg body weight: 150 ml fluid, 15 g mono- and disaccharides, 6 g lipids (corn oil), 2.7 g amino acid mixture—containing a reduced amount of threonine and no glycine or serine—, mineral salts and vitamins;

(c) ursodesoxycholic acid (UDCA), up to 6 mg kg

During the entire period, serum glycine, taurine and bile acids, as well as urinary glycine, were regularly monitored.

Quantitative amino acid analysis was performed by automated column chromatography on a Pye Unicam HPLC system equipped with an anion exchanger Shodex CX Pak column. Bile acids were determined by the enzymatic technique described by Mashige et al. (1976).

The 225-day long observation (Figure 1) was divided into eight periods, corresponding to the different therapeutic assays.

![Figure 1](image-url)

**Figure 1** Serum bile acids, taurine and glycine during the 225 days of the treatment.