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Tonic upward gaze as a first manifestation of atypical neonatal non-ketotic hyperglycinemia



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This 3610 g male term infant was born to a 30-year-old G1/P1 at 41 4/7 weeks of gestation after an uneventful pregnancy at another institution. Umbilical cord pH values, Apgar scores and adaptation were normal. His parents reported to be non-consanguineous and the family history was unremarkable.

At the age of 4 days, he was transferred to our neonatal intensive care unit because of periodic abnormal eye movements which had been observed since birth and consisted of episodes with a tonic upward gaze (Fig.1, movie). In addition, the infant was found to be hypotonic with a poor suck and to have dyskinetic movement abnormalities. The infant had no dysmorphic features. When he developed focal myoclonic jerks of his right arm, anticonvulsive therapy with phenobarbitone was started. EEG at the age of 10 days showed some multifocal epileptic activity in NREM-sleep with preserved background activity. During the episodes with tonic upward gaze, no epileptic discharges could be registered.

A metabolic disorder was considered and an extensive diagnostic work-up was initiated. Serum concentrations of glucose, electrolytes, lactate, creatinkinase, acylcarnitine and pipecolic acid were all within normal limits. Urine organic acids were also normal. The only abnormal finding was an elevated urine concentration of the amino acid glycine (1758 mmol/ml creatinine; normal range 283-1097 mmol/mol creatinine).

CASE REPORT

Imaging studies, including cerebral ultrasound and MRI, showed no abnormalities.

After 9 days of hospitalization, our patient was discharged home and followed as an outpatient in the Department of Neuropediatrics. Confirmatory measurements of glycine concentrations in serum and CSF were performed. Two out of three tests showed elevated levels of glycine in plasma and CSF. The CSF:plasma glycine ratio was abnormal with values of 0.08 and 0.06 (normal < 0.02). These results were consistent with a diagnosis of non-ketotic hyperglycinemia.

Molecular genetic analyses of the testable glycine cleavage complex genes were performed (Ch. Saban, CHU, Lyon, France) and confirmed the suspected diagnosis of an atypical non-ketotic hyperglycinemia encephalopathy. There was a homozygous c.886C>T-mutation (p.Arg296Cys) in exon 8 of the amino-methyl-transferase-(T-protein) gene (Fig.2). Both parents were heterozygous for this mutation.

Over the first few weeks of life, the abnormal tonic upward gaze changed to an intermittent hypersaccadic downbeat nystagmus and finally disappeared entirely. The patient continued to be seizure-free and phenobarbitone was discontinued at the age of two months. At the age of 9 months, there was a transient episode of choreoathetosis with an encephalopathic EEG during an episode of a RSV infection. Currently, at the age of 18 months, the boy shows still some muscular hypotonia, moderate coordination abnormalities and a mild developmental delay while the dyskinetic movements have decreased significantly. He receives physical therapy and an early occupational intervention therapy.

Patient with tonic upward gaze (screenshots, to download movie click movie button below).



Fig. 1

DISCUSSION

Non-ketotic hyperglycinemia (NKH), also known as glycine encephalopathy, is an autosomal recessive disorder which is caused by defects of subunits of the glycine cleavage system. As a consequence, large quantities of glycine accumulate in all body tissues, including the brain where neurotoxicity occurs. It is increasingly recognized as a heterogeneous disorder. The majority of patients presents in the neonatal period. The incidence of NKH is estimated to be about 1:60'000 (1).

The typical neonatal manifestation includes hypotonia, lethargy, apnea, hiccups and seizures (myoclonic jerks, EEG with burst suppression) and can lead to death. The long-term outcome of classical neonatal-onset NKH is often very poor with survivors suffering from severe disability, mental retardation, seizure disorder, quadriplegia, spasticity and irritability that may be difficult to control. Most affected children die before the age of 1 year.

A transient variant of neonatal NKH has been described in a number of patients presenting with apparently classical NKH but in whom the biochemical abnormalities of high glycine levels in blood and CSF have normalized within several weeks (1).

The infantile form of NKH is characterized by hypotonia, neurological disability and seizures. The manifestations of atypical forms of NKH range from milder forms that manifest in late infancy or even adulthood



to rapidly progressive and severe disease. Features include seizures, developmental delay, hyperactivity, spastic diplegia, optic atrophy, vertical gaze palsy and ataxia or chorea (2-4).

Some patients with NKH have structural brain abnormalities such as agenesis of the corpus callosum, gyral malformations, demyelination, hydrocephalus and white matter hyperintensity on MRI (1, 5).

In typical NKH, glycine concentrations are elevated in urine, plasma and CSF. However, in patients with atypical forms of the disease, plasma and urine glycine levels can be normal and only abnormal CSF:plasma glycine ratios will lead to diagnosis. The disease can be confirmed either biochemically (deficient glycine cleavage system (GCS) activity in the liver) (3, 6) or by molecular genetic testing. A new method to measure GCS activity, the C-glycine breath test, has recently been reported and is based on the fact that the metabolism of glycine leads to CO2 production (7).

GCS is a multienzyme complex located on the inner mitochondrial membrane of liver, kidney, brain, and placenta. It consists of four individual protein components (P: pyridoxal phosphate-dependent glycine decarboxylase (involved in 75% of patients with NKH), H: lipoid acid-containing hydrogen carrier protein) T: tetrahydrofolate-dependent protein (involved in 20% of patients with NKH), L: lipoamide dehydrogenase).

Protein	Enzyme	Prevalence of mutation in NKH patients
Р	GLDC Glycine-decarboxylase	70-75%
Т	AMT Aminomethyltrans- ferase	20%
Н	GCSH Glycine-cleavage- system H	< 1 %
Unknown	Unknown	5%

Table

Proteins of the GCS multienzyme complex involved in NKH.

Glycine is an excitatory neurotransmitter acting via N-methyl D-aspartate (NMDA) receptors in the cortex and an inhibitory neurotransmitter in the brainstem and spinal cord (4, 5, 8). The neurologic damage is mostly attributed to NMDA receptor overstimulation (7).

Currently, there is no causal therapy for severe NKH. Reducing glycine plasma concentration by dietetic measures and sodium benzoate therapy can be attempted. An other approach consists of blocking NMDA receptors: Potential antagonists are felbamate, ketamine and dextromethorphan. There are reports of a beneficial effect on glycine inhibitory symptoms such as hypotonia and apnea, as well as glycine excitatory symptoms such as seizures (2, 7). No treatment has been shown to prevent neurologic sequelae (7).

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