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Case study

A novel *AMT* gene mutation in a newborn with nonketotic hyperglycinemia and early myoclonic encephalopathy

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ABSTRACT

Early myoclonic encephalopathy (EME) presents in neonatal period with erratic or fragmentary myoclonus and a burst-suppression electroencephalography (EEG) pattern. Nonketotic hyperglycinemia (NKH) is the most common metabolic cause of EME and genetic testing confirms the diagnosis of NKH in around 75% of the patients with a clinical diagnosis of NKH. Three genes are known to cause NKH.

Here we describe a case of EME caused by NKH in which a new mutation in aminomethyltransferase (*AMT*) gene has been detected.

1. Introduction

Early myoclonic encephalopathy (EME) presents in neonatal period with erratic or fragmentary myoclonus and a burst-suppression electroencephalography (EEG) pattern. Inborn errors of metabolism comprise the most common cause (especially nonketotic hyperglycinemia), but other amino-acid and acid disorders such as propionic aciduria and D-glycericacidemia can be involved.[1] Nonketotic hyperglycinemia (NKH) is an autosomal recessive disorder and is caused by a glycine cleavage system (GCS) deficiency that leads to accumulation of glycine in all body compartments. Three genes are known to cause NKH: glycine decarboxylase (*GLDC*) *gene* (accounting for the 70–75% of disease); aminomethyltransferase (*AMT*) gene (accounting the 20% of disease), and hydrogen carrier protein (*GCSH*) (accounting for <1% of disease).[2]

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Here we describe a case of EME caused by NKH in which a new mutation in *AMT* gene has been detected.

2. Case study

A male neonate was born at 40 3/7 weeks gestation by consanguineous Turkish parents. Pregnancy and delivery were uneventful. Physical examination showed a nondysmorphic neonate. During the first day after birth poor feeding, progressive hypotonia, lethargy, hiccups, myoclonus, and finally respiratory insufficiency developed. Cranial ultrasound examination performed on admission showed hypoplasia of the corpus callosum. Infection index (reactive C protein and blood culture), blood electrolytes, blood glucose, serum ammonia and lactate levels were normal. Video-EEG recording indicated a burst-suppression-like pattern, firstly associated with erratic myoclonus and soon after with massive myoclonic jerks and tonic spasms (Fig. 1). A diagnosis of EME was advanced and thus a metabolic disease was suspected. Metabolic investigations showed increased plasma glycine levels (1572 mmol/l), with a liquoral glycine value of 286 mmol/l and a CSF/plasma ratio of 0.18 (normally <0.02), leading to the diagnosis of NKH. Magnetic resonance imaging (MRI) of the head showed hypoplasia of the corpus callosum. Proton-MRS with extended echo time showed biochemical evidence of high cerebral glycine levels with decreased N-acetylaspartate.

The parents were informed of his progressive encephalopathy, and with their consent, at six days of age he started standard therapy with sodium benzoate (500 mg/kg/day), dextromethorphan (3.5 mg/kg/day) and phenobarbital (5 mg/kg/day). A decrease of glycine level and a mild increase of CSF/plasma glycine ratio were observed after 10 days. Despite these changes in glycine levels and the administration of levetiracetam and phenobarbital, EEG continued to show a suppression-burst pattern and the neonate continued to present myoclonic jerks and tonic epileptic spasms for about twenty days (Fig. 1).

A later molecular analysis showed homozygous mutation in *AMT* gene with substitution in exon 7: c.793C > T responsive for the placement of an arginine by a cysteine at position 265 on the protein (p.Arg265CYS). This is a novel mutation and because it affects a conserved amino acid, it was considered pathogenic. Parental testing confirmed that this mutation was maternally and paternally inherited in heterozygous state.

He was discharged home after two months with tube feeding and treatment with oral sodium benzoate 500 mg/kg/day and dextromethorphan 10 mg/kg/day. At 6 months of age no myoclonias and tonic spasms were noticed and EEG showed a pattern of delta and theta activity with isolated focal spikes (Fig. 2).

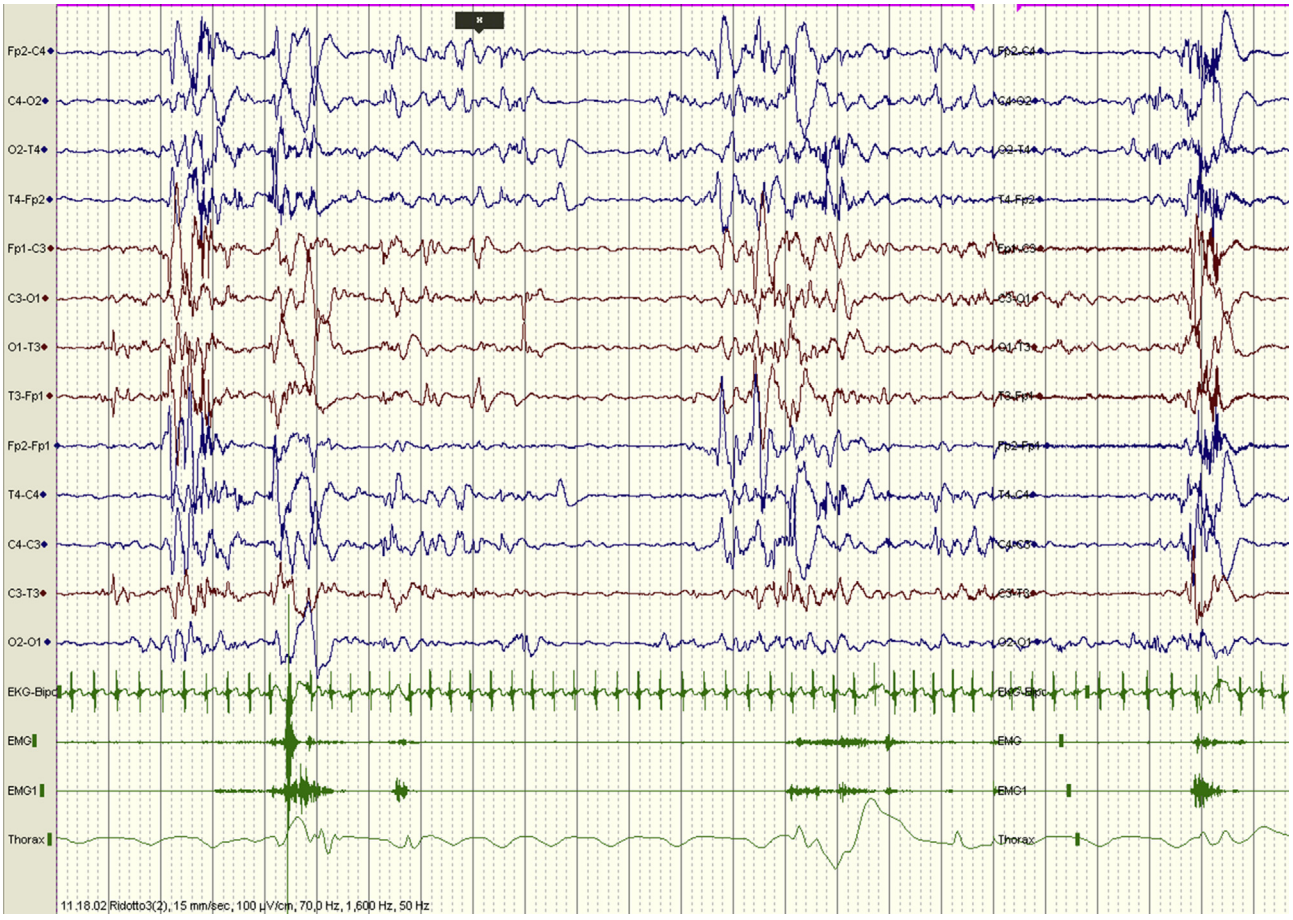

Fig. 1 – The EEG recording shows a suppression-burst pattern characterized by a succession of bursts of paroxysmal activity separated by episodes of flat or low-amplitude tracing.