

Neonatal Non-Ketotic Hyperglycinaemia in a 2 Day Old Baby

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Abstract

Transient neonatal non-ketotic hyperglycinaemia (NKH) is a rare metabolic disorder in neonates which is indistinguishable from its classic form during the neonatal period. To our knowledge, only a few cases (about 14) of transient neonatal hyperglycinaemia have been reported. We report a 2 day old neonate who presented with clinical (seizure) and biochemical (raised CSF/Plasma glycine ratio) features of neonatal NKH. EEG on day 2 of life showed burst suppression pattern; hiccups noted during this EEG did not show any cortical origin except for concurrent artefacts. Biochemical features normalised by 4 weeks of age; EEG was encephalopathic at 4 and 17 week (current age). Infant currently has truncal hypotonia and developmental delay. There is no case report describing concurrent hiccups during EEG and timing of encephalopathy appearance on EEG, which in our case is 3-4 week of age.

Keywords: Neonate; Seizure; Hyperglycinemia; Electroencephalography

Background

Glycine encephalopathy (GCE) (*OMIM 605899*), also known as non-ketotic hyperglycinaemia (NKH), is a disorder characterised by excessive accumulation of glycine in all tissues, especially central nervous system (CNS). This is due to defect in glycine cleavage system (GCS); this system has P-protein, T-protein, H-protein and common L-protein [1].

Glycine functions as excitatory neuro-modulator at N-methyl-D-aspartate (NMDA) receptor at cortex and forebrain [2]; excess glycine activity leads to intractable seizures, neuronal injury and subsequent cell death. Glycine also acts as neurotransmitter on glycinergic receptor at spinal cord and brain stem; stimulation of these receptors has inhibitory effect leading to muscular hypotonia, neonatal apnoea and hiccups [1,3]. There are several forms of NKH, neonatal form being the most severe phenotype which presents within first few days after birth. Neonatal NKH can be classified into classic neonatal forms and Transient neonatal forms with varied outcome [3]. Various biochemical options (liver, lymphoblast, mutation analysis) are available to measure residual glycine cleavage system (GCS) activity [3]. Transient NKH has been reported with homozygosity for mutation leading to significant residual GCS activity or with heterozygosity [3]. There is optimism that for many patients with transient NKH a detailed molecular investigation will give a DNA diagnosis [3]. Practical difficulties in making a reliable laboratory diagnosis of transient NKH remain [4]. Nevertheless, early recognition with the help of available investigations can be extremely helpful, to help decide further management [5,6]. We report a neonate who presented with features suggestive of glycine encephalopathy (NKH) at 2 days of age; EEG and MRI were abnormal at this age; EEG continues to show features of encephalopathy at current age of 17 weeks. However, biochemical abnormalities returned to normal before 3 weeks of age.

Case Report

A male infant was born to non-consanguineous parents, at term, by caesarean section for failure to progress; mother was healthy with uneventful antenatal scans and pregnancy. Apart from 5 inflation breaths, baby did not need any resuscitation and transferred to postnatal ward. The APGAR were 6, 7 and 9 at 1st, 5th and 10th minutes respectively. Birth weight was 2810 gm (9th to 25th centile), head circumference 32.5 cm (above 9th centile) and length 51 cm.

At 27 hours of age, he developed seizures (abnormal posturing, cyclic movements of limbs and lip smacking) needing admission to

neonatal intensive care unit. Seizures had settled within a week; the baby was floppy but no seizure was noted on 12th day of age; hence, he was discharged home. Clinical examination at 8th week of age had shown truncal hypotonia; weight was at 25th-50th centile, head circumference at 2nd-9th centile. The infant did not have further seizures or spasms at 8 week of age; however, he has truncal hypotonia, poor head control and no recognisable social smile at 17 weeks of age. He did not receive sodium benzoate.

Investigations

Full septic screen was negative. Amplitude integrated EEG on day 2 showed suspicious seizure activity, needing standard EEG. Standard EEG on day 2 of age shows burst suppression pattern (Figure 1). Hiccups with concurrent artefacts on EEG were noted (Figure 2). Diffusion MRI done on 3rd day of age showed abnormality involving myelinated area of brain from cortex down to pons; basal ganglia was involved but thalamus and part of caudate nuclei are spared (Figure 3). Magnetic resonance spectroscopy is not done. CSF/Plasma glycine ratio was 0.04 on day 2 of life; this had normalised on repeat assay at 24th day of age. Other metabolic screens (Serum ammonia, urine organic acid, plasma branched chain amino acids) were normal done on day 2. Repeat extensive metabolic investigations at 4th week of age yielded no other abnormality. CSF PCR for meningococci, pneumococci, varicella zoster virus, herpes simplex virus, enterovirus, parechovirus were negative; blood and urine cyto megalovirus PCR was negative. Blood, urine and CSF were negative for bacterial cultures. Repeat EEG was performed at 4th week of age which showed encephalopathic pattern, but no epileptiform activity seen. Further repeat EEG at current 18th week of age continued to show encephalopathic pattern.

Differential Diagnosis

Differential diagnoses of sepsis, CNS infection were considered and investigated as mentioned. Hypoxic ischaemic encephalopathy is less likely in view of presentation and history.

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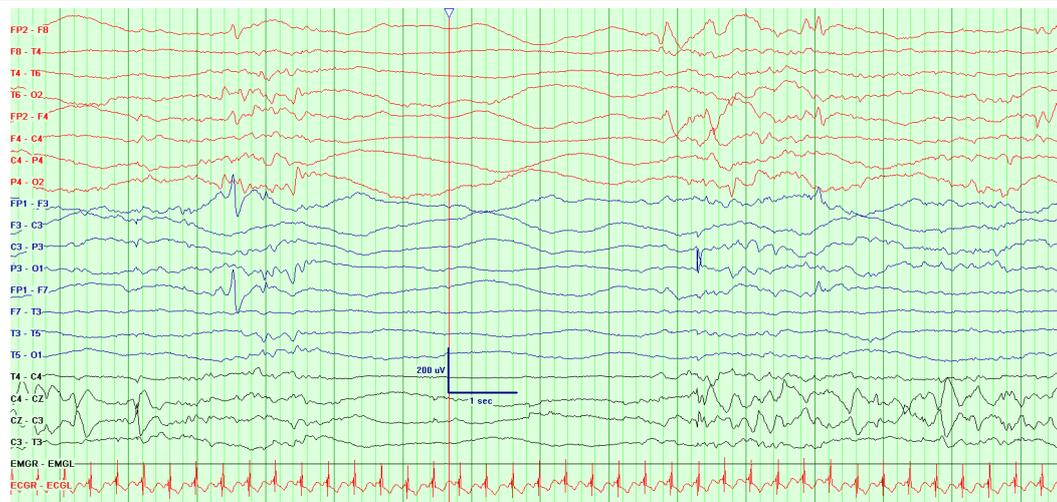


Figure 1: EEG background showing Burst-suppression pattern. Burst-suppression pattern is well described in neonatal NKH. Note bursts of background activity followed by suppression.

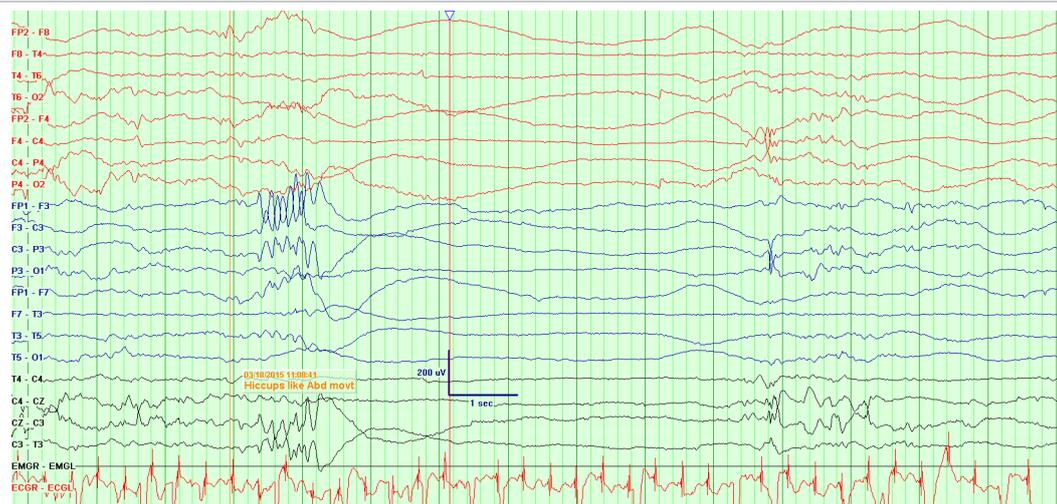


Figure 2: No EEG correlates for hiccups. Hiccups noted during EEG recording on day 2 of life as shown in video. These do not show any EEG correlates except for artefacts.

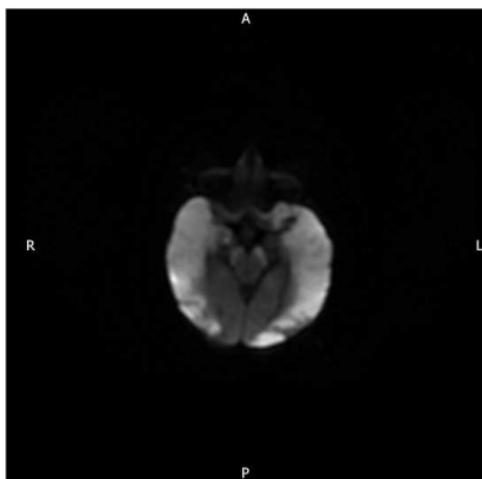


Figure 3: Diffusion MRI on day 3 of life. Diffusion MRI brain shows hyper-intensity in myelinated areas; brain stem also shows hyper-intensity in these areas.

Treatment

He did not receive sodium benzoate for raised glycine since glycine had normalised on repeat testing. He did receive phenobarbitone for seizure control during first week. He is not on any anticonvulsant or medication currently.

Outcome and Follow-Up

The infant did not have further seizures or spasms at 8 week of age; however, he has truncal hypotonia, poor head control and no recognisable social smile at 17 weeks of age.

Discussion

Non-ketotic hyperglycinaemia (NKH) has varied presentation and outcome. Clinical presentation of transient glycine encephalopathy (also called transient NKH) is not different from other forms; however, there are management implications such as treatment with benzoic acid which is less likely to be needed in transient forms [5]. EEG can be a helpful tool both during early neonatal period and later in the course [6-11].

Learning Points/Take Home Messages

- Neonatal NKH is a rare condition which presents with seizure and hiccups early in life.
- Early recognition can help to prognosticate and guide further investigations.
- EEG can be a helpful tool in addition to MRI.
- Hiccups in NKH do not have any surface EEG correlates.
- MRI can show bilateral changes in myelinated area (vacuolating myelinopathy).

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