



'Fifth Day Fits' (FDF) – Biotinidase Deficiency is Probably the New Name

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Abstract

Neonatal Seizures, the most critical of neonatal neurologic dysfunction, has aetiology of varying prognoses. The diagnosis of underlying aetiology is most critical. With use of genetic studies, better imaging technologies, better cortical electrical activity mapping and biochemical advancement, every attempt in diagnosing a cause is made.

Keywords

Neonatal Seizures, Biotinidase Deficiency, Metabolic Screening

Introduction

'Fifth day fits', first described by Dehan et al in 1977 [1]. They described 20 neonates with convulsions in a paper entitled "Les convulsions du cinquième jour: un nouveau syndrome?" ("Fifth day's fits: a new syndrome?"). It was described as clonic in nature, occurring on day 5 of life, lasting for 24-48 hours, but refractory to anticonvulsants and total recovery thereafter without morbidity. Similarly, Pryor et al [2] in early 1980s observed surge in Sydney, Australia and France. With no apparent cause, they are idiopathic in nature and are called as Benign Idiopathic Neonatal Convulsion (BINC). The concern on these being called benign was raised as 1989 [3], and thus needs to be differentiated from other neonatal seizure syndrome.

Most neonatal seizures occur in early days in life with most occurring in first 28 days for term and up to

corrected gestation of 44 weeks in preterm infants. Most being acute reactive or symptomatic in nature, only few have long term recurrence. Seizures in neonates are often the first sign of neurologic dysfunction, and are predictor of long-term cognitive and developmental impairment. Most seizures in the neonate are focal, although generalized seizures may happen. They could be subclinical, tonic, clonic, or myoclonic in nature.

Neonatal brain is immature and in a hyper excitable state. Seizures occur as large group of neurons undergo excessive, synchronized depolarization. The brain in neonatal period is physiologically on use dependent synaptogenesis and both synapse and dendritic spine at its peak density [4,5]. Further, excitatory neurotransmitter (eg, glutamate and its receptor subunits) are found in excess making them

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hyperexcitable [6,7]. Also, deficient inhibitory neurotransmitter (e.g. gamma amino butyric acid [GABA]), can further have paradoxical excitatory action by GABA due to delayed KCC2 chloride cotransporter [8,9]. Ion channel viz. K^+ channels are known to regulate excitability of neurons. Thus, mutations related to K^+ channels KCNQ2 and KCNQ3 responsible for seizure activity in developing brain.

Case-1

A term baby boy born to non-consanguineous parents with no significant family history – weighed 3.5 Kgs at birth and had good APGAR score and didn't require any resuscitation at birth. Baby was feeding well and both mom & baby were discharged home on day 3.

Day 5 baby was brought in to the Emergency as the parents noticed a generalised tonic-clonic seizure lasting for 3 minutes. There were no precipitating factors and on arrival baby's blood sugars were normal at 65 mg/dL. Sepsis screen was negative. Arterial Blood Gas (ABG) done at the time along with serum lactate & ammonia levels were within normal limits. An MRI brain done was reported to be normal. A single loading dose of Phenobarbitone was given and no further seizures were noted. Paediatric Neurologist review was done and the advice was to continue oral phenobarbitone for 6 weeks, despite the EEG being normal and the suspicion was it is "probably 5th day fits". As per the hospital policy, the baby has had newborn screening the results of which were awaited. Parents requested a second opinion from a Paediatric Neurologist from a different city – and by that time the results of the newborn screening showed all the results being normal except biotinidase screening showing possible deficiency (with the biotinidase enzyme activity showing levels of 0.014 AU) and hence subsequent serum biotinidase assay was done – which was reported to show 0.40 nmoles/min/ml (with the normal range being 5.50 to 17.10) – confirming biotinidase deficiency – and the baby was commenced on oral biotin supplementation and currently baby is 5 years old with no further seizures and the development being completely normal.

Case-2

A term female baby weighing 2.9 Kgs was born by normal vaginal delivery to non-consanguineous parents, was feeding well and discharged home at 48 hours of age. Baby had mild icterus and no other risk factors. Presented on day 5 with neonatal seizures – but the routine newborn screening revealed biotinidase deficiency (with levels of biotinidase enzyme activity being 0.022 AU) with all the other screening by TMS (Tandem Mass Spectrophotometry) being normal – and later confirmed with serum biotinidase assay with levels being 0.36 nmoles/min/ml (with the normal range being 5.50 to 17.10) and hence no imaging was done – baby was commenced on biotin supplements and currently baby at the age of 2 years is doing well with no further seizures – on biotin supplementation.

Case-3

15 days old baby boy was brought to our hospital for a second opinion. The baby was born elsewhere by normal vaginal delivery with APGAR scores of 8 & 9 at 1 and 5 minutes respectively. Birth weight was 2.890 Kgs. Baby was doing well in the first few days. Breast fed and baby was feeding well. On day 5 baby was noted to have jerks of the whole body – when they were seen by a local Paediatrician – who checked the baby – weight being 2.69 Kgs. Mild jaundice with serum bilirubin being (8.9 mg/dL) and serum calcium, magnesium and blood sugar were all within normal limits. The local Paediatrician had organised EEG & MRI brain both of which were reported to be normal. After all these, the baby had been commenced on oral phenobarbitone. Parents brought the baby to see us – clinically the baby was normal. There was no family history of epilepsy or any other genetic disorders. Pregnancy had been uneventful. Hence as per our hospital policy we explained the need for newborn screening and advised the same. Parents got the newborn screening done – which was reported to be normal for congenital hypothyroidism, Glucose-6-Phosphatase Dehydrogenase (G6PD) Deficiency, 17 (OH) progesterone, Immunoreactive trypsin (for cystic fibrosis), amino acid and organic acid disorders – but was showing biotinidase deficiency (with levels of biotinidase enzyme activity being 0.012 AU) – and later confirmed with serum biotinidase assay with levels being 0.28 nmoles/min/ml (with the normal range

being 5.50 to 17.10). Baby was commenced on oral biotin supplements and was stopped phenobarbitone. Currently baby is 4 years old and doing well – both mentally and developmentally with no seizures.

Diagnosing Neonatal Seizures

It is more of a clinical suspicion, confirmed using continuous electroencephalogram (EEG) [10,11]. EEG study is usually gold standard for diagnosing neonatal seizures [10]. The 2011 *American Clinical Neurophysiology Society Guidelines [12] on Continuous EEG Monitoring* lists six conditions in which carry a high risk for seizures; encephalopathy after hypoxia (including perinatal asphyxia and in the setting of cardiac or pulmonary risks for hypoxia), CNS infection, intracranial hemorrhage, inborn errors of metabolism [13], perinatal stroke and genetic disease predisposing the infant to CNS malformations.

Computer tomography (CT) brain scan is often adjunctive to ultrasound. Last-generation CT brain scan images are of high resolution, and can be generated within seconds. CT brain can accurately detect haemorrhage, infarction, gross malformations and ventricular pathologies, but has low sensitivity in conditions such as abnormalities of cortical development where Magnetic Resonance Imaging (MRI) is much superior. In neonates, cortical abnormalities are detected with T2-weighted images, and brain maturation of T1-weighted images [14]. However, MRI interpretation requires consideration of the normal developmental and maturational states of preterm and term brains.

Biochemical Investigations

With the use of tandem mass spectroscopy, many of rarer causes of seizures are now becoming evident, especially the metabolic causes which present generally within 72 to 96 hours of life with seizures. Biochemical investigations have shown some of these so called 5th day fits are actually either due to Biotinidase deficiency or some other deficiencies. As more and more new modalities of investigations which are simpler and can be done on newborns are being discovered/invented – we are finding that 5th day fits are not what we used to think they are!

Biotinidase deficiency is an autosomal recessive disorder caused by a mutation in the gene (BTD gene), which allows for the production of the enzyme that separates the essential vitamin, biotin, making it available for the body's metabolism.

The BTD gene has been traced to the long arm of chromosome 3 at locus 3p25. Babies may be born without signs of biotinidase deficiency, but the symptoms become apparent after the first few weeks or months of life. Chief characteristics include weak muscles (hypotonia), seizures, hair loss (alopecia), an inflammatory skin rash (eczema), developmental delays, and lactic aciduria – but by the time these symptoms appear baby might have had other neurological problems. Earlier the diagnosis the better the prognosis. The famous quote in Baily & Love's textbook of surgery – “Your eyes can't see what your mind doesn't know” – probably answers the lack of awareness of the causes of 5th day fits in the past. In the modern neonatal medicine, is there a role for “5th day fits” or should we say Neonatal seizures – probably idiopathic? We present the above 3 cases to probably make the treating Paediatrician think of screening for biotinidase deficiency [15,16] in any baby who presents with seizures in otherwise healthy baby. We may be missing quite a few cases of biotinidase deficiency because we are not thinking of it so we are not investigating the babies with seizures.

Conflict of Interest

All authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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