Open Access

SCHOLARENA

Journal of Pediatric Disorders and Neonatal Care

CASE REPORT

Rigidity with Multifocal Seizure Syndrome, Lethal Neonatal in a Lebanese Neonate. A Rare Case Report

Skafi O[1], Fawaz A[1], Merhi BA[1*], Jouni H[1], Mansour S[1], Harb R[2], Nacouzi R[1] and Dabaja H[1]

[1]*Department of Pediatrics, Lebanese University, Faculty of Medical Sciences, Beirut, Lebanon*
[2]*Department of General Surgery, Lebanese University, Faculty of Medical Sciences, Beirut, Lebanon*

[*]**Corresponding author:** Merhi BA, Department of Pediatrics, Lebanese University, Faculty of Medical Sciences, Beirut, Lebanon, Tel: +96170722205, E-mail: bassemaboumerhi@gmail.com

Citation: Skafi O, Fawaz A, Merhi BA, Jouni H, Mansour S, et al. (2018) Rigidity with Multifocal Seizure Syndrome, Lethal Neonatal in a Lebanese Neonate. A Rare Case Report. J Pediatr Dis Neonatal Care 1: 106

Article history: Received: 23 April 2018, **Accepted:** 18 June 2018, **Published:** 20 June 2018

Abstract

Rigidity with Multifocal Seizure Syndrome, Lethal Neonatal is a neonatal epileptic syndrome OMIM 614498, presenting early in newborn life as drug resistant myoclonus, generalized rigidity and delayed milestones. This syndrome is strongly associated with mutations of the BRAT1 (Breast cancer 1-associated Ataxia Telangiectasia mutated activation-1 protein). In this report we present a case of a Lebanese male newborn with drug resistant convulsions since birth. The whole exome sequencing revealed a mutation in BRAT1 gene. To our knowledge this is the sixth reported case linking this clinical presentation to a homozygous BRAT1 mutation.

Keywords: Neonatal; Drug resistant; Seizure; Rigidity; BRAT1

Introduction

Rigidity and Multifocal Seizure Syndrome, Lethal Neonatal is an autosomal recessive disease, recently characterized, affecting neonates with epileptic encephalopathy, and manifesting as drug resistant seizure [1]. It is caused by mutation in BRAT1 (Breast cancer 1-associated Ataxia Telangiectasia mutated activation-1 protein), where only five cases were reported in the literature, linking this syndrome with a homozygous mutation of BRAT1 gene [1-4]. These five cases were in Amish, Arabic, Mexican and Turkish countries. They all have similar presentations with drug resistant myoclonic seizures associated with axial and limb rigidity. This case describes a Lebanese newborn with BRAT1 mutation linked to Rigidity and Multifocal Seizure Syndrome, Lethal Neonatal (RMFSL).

Case report

Our patient was an eight days old male newborn, born to a 21 year old mother Gravida one, Para one and Aborta zero, with first degree consanguinity between parents. His Apgar score at birth was 7 and 8 at 1 and 5 minutes respectively. His birth weight was 3400 g. First hours of life after birth the baby started to develop facial and peri-orbital myoclonic movements in association with upper extremities myoclonus so he was started on Phenytoin 20 mg/kg IV over 20 minutes because of persisted the abnormal movements Phenobarbital 20 mg/kg was added but by oro-gastric tube (OGT) being the IV form was out of order in that center; Then as maintenance therapy Phenytoin continued as 5 mg/kg/day IV divided Q12 hrs and Phenobarbital as 10 mg/kg/day per OGT divided Q12 hrs. Unfortunately the myoclonic movements persisted and aggravated by apneic spells so he was transferred under our care at day of life 8. He also was in a state of stupor; he had limb and axial hypertonia and rigidity. Myoclonus increased following tactile or auditory stimuli. He had no abnormal morphological features, no sucking reflex and deep tendon reflexes were hyperactive, which also initiates myoclonic jerks in the tested limb. Treatment initiated with phenobarbital and total parenteral nutrition. Workup taken: CBCD, CRP, ABG's, chemistries, Lactate, Ammonia, CSF studies with cell count and chemistries all were within normal range values. Blood and CSF amino acids, urine and CSF organic acids also were normal also. TORCH screening and tetanus antibodies turned out to be negative. Meanwhile EEG done and revealed low voltage background without abnormal epileptic discharges. Patient persisted to have continuous myoclonic seizures so Carbamazepine and Levetiracetam were added at their maximal doses. Brain MRI done at day of life 11 and was normal, it was scheduled to be repeated 3 months later. Pyridoxine, Pyridoxine 5 phosphates, coenzyme Q12 were started which also failed to control myoclonus. Midazolam was also tried and as a last resort a trial of Zonisamide at its maximal acceptable dose was given with no clinical improvement. Whole genome sequencing

analysis realized using Sureselect Human all Exon V6 kit, sequenced on illumine platform detected a known mutation Chr7 (GrCh37): g.2583389dupnm_001350626.1:c.638dup, p(val214 Glyfs*189) exon5 described by Puffenberger et al in 2012 which results in a frame shift mutation starting at codon 214 and ending at a stop Condon 188 positions downstream [1]. Patient lived till 3 months of age developed many times aspiration pneumonias and passed away. Mother and father were scheduled for genetic counseling.

Discussion

Early neonatal myoclonus has a narrow differential diagnosis, the resistant type of seizure is suggestive of rigidity with multifocal seizure syndrome, lethal neonatal. Yalcin et al describe a case of RMFSL similar to ours that survived until 11 months of age and died of multi-organ failure [4]. Their case was also homozygous for BRAT1 mutation but had different one. No dysmorphic features found in our patient in contrast to the case reported by Saunder et al where in a Mexican family they have bitemporal narrowing, nasal flattening and upward slanting palpebral fissure [2]. Another Arab family in which BRAT1 mutation causing RMFSL described by Straussburg et al with normal first brain MRI similar to our case and same clinical presentation of myoclonus, rigidity and hyper tonicity, but earlier death and a different mutation [3]. Van de Pol LA et al described 3 others siblings with same mutation and same clinical presentation as our case [5]. Heterozygous BRAT1 mutation has been described in the literature presenting as a milder clinical picture with longer survival [6,7]. BRAT1 encodes for proteins that influence BRCA1 gene and controls the cell cycle and its response to DNA damage. BRAT1 is also considered to be involved in cell growth and hypo ptosis [3].

Conclusion

In conclusion BRAT1 gene mutations should be considered in cases of early onset neonatal seizure especially drug resistant myoclonus.

Acknowledgement

We are immensely grateful to Scholarena, open access publishers for their support in dissemination of our work. Authors acknowledge the immense help received from the Scholarena whose articles are cited.

Reference

1. Puffenberger EG, Jinks RN, Sougnez C, Kristian Cibulskis, Rebecca A Willert, et al. (2012) Genetic mapping and exome sequencing identify variants associated with five novel diseases. PLoS One 7: e28936.

2. Saunders CJ, Miller NA, Soden SE, Dinwiddie DL, Noll A, et al. (2012) Rapid whole-genome sequencing for genetic disease diagnosis in neonatal intensive care units. Sci Transl Med 4: 154ra135.

3. Straussberg R, Ganelin-Cohen E, Goldberg-Stern H, Tzur S, Behar DM, et al. (2015) Lethal neonatal rigidity and multifocal seizure syndrome - report of another family with a BRAT1 mutation. Eur J Paediatr Neurol 19: 240-2.

4. Celik Y, Okuyaz C, Arslankoylu AE, Ceylaner S (2017) Lethal neonatal rigidity and multifocal seizure syndrome with a new mutation in BRAT1. Epilepsy Behav Case Rep 8: 31-2.

5. Van de Pol LA, Wolf NI, van Weissenbruch MM, Stam CJ, Weiss JM, et al. (2015) Early-Onset Severe Encephalopathy with Epilepsy: The BRAT1 Gene should be added to the List of Causes. Neuropediatrics 46: 392-400.

6. Hanes I, Kozenko M, Callen DJ (2015) Lethal neonatal rigidity and multifocal seizure syndrome-a misnamed disorder? Pediatr Neurol 53: 535-40.

7. Mundy SA, Krock BL, Mao R, Shen JJ (2016) BRAT1-related disease-identification of a patient without early lethality. Am J Med Genet A 170: 699-702