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Case Report

Lethal neonatal rigidity and multifocal seizure syndrome with a new mutation in BRAT1

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ABSTRACT

Rigidity and Multifocal Seizure Syndrome, Lethal Neonatal (RMFSL) (OMIM# 614498) is a rare and recently characterized epileptic encephalopathy that is related to variants in the BRAT1 gene (Breast Cancer 1-associated ataxia telangiectasia mutated activation-1 protein). In this report, an RMFSL case, who died in the 10th month of the life, with rigidity, drug-resistant myoclonic seizures in the face and extremities, with, significant motor delays is presented. The exon sequence was determined and a new homozygous variant (C.2230_2237dupAACATGC) was detected. This RMFSL case with a homozygous variant in the BRAT1 gene, is the fourth one in the literature and the first one being reported from a Turkish family.

1. Introduction

Rigidity and Multifocal Seizure Syndrome, Lethal Neonatal (RMFSL) (OMIM# 614498) is a recently defined autosomal-recessive epileptic encephalopathy, which is characterized by drug-resistant seizures, and rigidity [1,2]. This syndrome is thought to be caused by variants in BRAT1 (Breast Cancer 1-associated ataxia telangiectasia mutated activation-1 protein) gene [1–3]. In the literature, to the best of our knowledge, there are only three case reports suggesting a relation between this syndrome and a homozygous variant in BRAT1 gene. These cases were reported in the Amish, a Mexican family, and an Arabic family. Similar to each other, these cases with RMFSL a diagnosis and a homozygous variant in BRAT1 gene were reported to have drug-resistant seizures, axial and extremity rigidity and delay in the increase of head circumference in the initial days after birth. Additionally the lethality for the subjects in the first six months of the life were also reported [1–3]. This case, diagnosed as RMFSL with a homozygous variant in BRAT1 gene, is the fourth one in the literature and the first one being reported from a Turkish family. In addition, in this case a new variant, not reported earlier, was found to be involved.

2. Case report

A 27-day-old baby born of a consanguineous marriage in a Turkish family was admitted to our center from another hospital because of drug-resistant myoclonic seizures. He had no EEG monitoring before admission to our hospital. The patient history revealed occurrence of respiratory distress immediately after birth and drug-resistant seizures despite treatment with phenytoin, phenobarbital, and midazolam. The baby was receiving medical care in a neonatal intensive care unit (NICU) since birth. He was a male twin (fraternal), and the mother reported abnormal movements of him with respect to her female baby in the late weeks of the pregnancy. The birth was a cesarean-section. Apgar scores in the first and fifth minutes were 8/8, birth weight was 2200 g (10–25%), head circumference was 30 cm (<10%) and the height was 43.5 cm (10–25%). The weight at evaluation in our center was 2320 g, the height was 45 cm and the head circumference was 31 cm. Anterior fontanelle was open and sized 1 × 1 cm. The baby, in response to touch, showed myoclonic seizures in the extremities and face. He had hypertonia and resistance during extension in his arms. He did not have dysmorphic facial features. His deep tendon reflexes were hyperactive and had four to five beats of clonus. He had difficulty in swallowing, needed suctioning frequently and was started to be fed by an orogastric tube. Complete blood count, peripheral blood smear, biochemical analyses, C reactive protein, procalcitonin, blood gas, lactate, ammonia, tandem mass, cranial magnetic resonance imaging (MRI), cranial MRI spectroscopy, cerebrospinal fluid (CSF) glycine/plasma glycine ratio, CSF glucose/blood glucose levels, serum amino acid, and urine organic

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acid analyses were all normal, and TORCH test results were negative. There was no growth in blood and CSF cultures. EEG showed 4–6 Hz theta background activity, bilateral frontotemporal sharp waves and 8–10 Hz ictal rhythm during clinical seizures. Phenytoin, phenobarbital, and midazolam treatments were continued but there was no improvement in myoclonic seizures. Pyridoxine, levetiracetam, clonazepam, vigabatrin, and topiramate were tried with without success and the baby was intubated for apnea apneic. Initial cranial MRI was normal; however, cerebral and cerebellar atrophy and thinning of the corpus callosum were noted in the cranial MRI obtained three months later. Besides the whole exome sequencing analysis performed by Illumina Nextseq 500 platform detected a new homozygous variant (NM_152743.3:c.2230_2237dupAACACTGC) the in BRAT1 gene. This change results in a frameshift variant and early stop codon (p. S747Tfs*36). In vitro evaluation of the variant with variant Tester software revealed that this change is the main cause of the disorder. BRAT1 protein consisted of 821 amino acids and this variant causes defect in the 747th amino acid and leads to the cessation of protein synthesis 36 amino acids later. These findings confirmed RMFSL. In addition, mother and father were also found to be heterozygous for the same variant. Genetic testing was not performed in the sibling since she had no clinical findings and she a was fraternal twin. When the child was 5 months old she was still intubated and feeding with an orogastric catheter so that tracheostomy and gastrostomy were performed and after that she was transferred to a pediatric intensive care unit (PICU). The seizures and involuntary movements increased and the rigidity persisted until the tenth month. He had dropping head circumference percentiles (<3%) and neurological motor delay. The patient died due to multiorgan failure at the age of 10 months.

3. Discussion

RMFSL was first reported in three newborns from three related families in the Amish Society by Puffenberger et al. [1] in 2012. They reported a child with intrauterine jerks, delayed head circumference growth, axial and extremity rigidity, and unresponsiveness to the antiseizure drugs. In addition, all the cases showed no developmental improvement until death and two cases had a homozygous variant the in BRAT1 gene in the whole exome sequencing analysis. There are several similarities between our patient and their cases [1]. In the present case, the mother and father were 1st cousins and the mother reported abnormal fetal movements in during late pregnancy and suggests the possibility of jerks in the intrauterine period. Our patient's head circumference remained small. Rigidity, focal jerks, and myoclonic seizures persisted throughout his life. Antiseizure drugs were not effective. There was neurodevelopmental delay and the baby died at the 10th month. Our patient had a homozygous variant in the BRAT1 gene, which was a new one and different from the variant reported by Puffenger et al. [1].

Saunders et al. [2] reported a new RMFSL case in the same year after the first report by Puffenger et al. [1]. They reported a female newborn in a Mexican family with a consanguineous marriage and reported that the baby had drug-resistant seizures soon after birth, hypertonicity, cortical thumbs, clonus, and twitching of the face. At the fifth month, dysmorphic findings such as bitemporal narrowing, nasal flattening, up-slanted palpebral fissures, and up-lifted ear lobes with redundant helices were detected and the baby was reported to die on the 54th day. In this case, a homozygous variant in the BRAT1 gene was also reported. In our case, similar to that reported by Saunders et al. [2], there were drug-resistant seizures, hyperreflexia, clonus, focal jerks, and hypertonicity. However, there were no dysmorphic findings reported by them.

The third case with a homozygous variant in the BRAT1 gene was reported by Straussberg et al. [3] in 2015. They reported two children, born of a consanguineous marriage in an Arab family, with apneic episodes interpreted as seizures, hypertonicity, and hyperreflexia. Although, the brain imaging was normal the patients had impaired neurodevelopmental outcomes. Both the babies died at the 5th and 6th months. The clinical findings of our case and that reported by Straussberg et al. [3] were similar. In addition, the cranial MRI taken in the early period was also normal similar to that reported by Straussberg et al. [3]. However, cranial MRI taken at the fourth month showed changes in the brain consistent with atrophy. This finding indicates that RMFSL causes progressive changes in the brain and even if brain imaging is normal initially, pathologic changes may appear in the upcoming period.

As far as we know in the literature, there are only three case reports of a homozygous variant in the BRAT1 gene [1–3]. Furthermore, three case reports with clinical similarity to RMFSL and with a heterozygous variant in the BRAT1 gene were also published [4–6]. One of these reports was about two brothers with hypertonicity, drug-resistant seizures, apneic episodes, dysmorphic face, cerebral and cerebellar atrophy in brain imaging and the subjects died at the 3rd and 12th months [4]. The other two case reports with a heterozygous variant in the BRAT1 gene had milder clinical courses than classical RMFSL. They were reported to be 4 and 6 years old and still alive [5,6]. It can be assumed, from the previous reports that homozygous variants in the BRAT1 gene possibly causes more severe clinical findings and shorter life expectancy than heterozygous variants.

Interestingly, frameshift variants have frequently been detected in RMFSL cases [1–6]. A frameshift variant was also detected in our case. The distribution of the variants suggests that the variants that affect the end parts of the proteins have the major role in the pathogenesis of the disease. The variant, s747tfs*36, which we detected, involves the largest number of codons. And it shows that a frameshift variant that affects the amino acids between 747 and 821 may cause RMFSL.

In conclusion, RMFSL should be considered in the differential diagnosis in the evaluation of newborns with drug-resistant seizures and rigidity; and BRAT1 gene variants should be investigated in suspected cases.

Conflict of interest

All the authors have no conflict of interest.

References

[1] Puffenberger EG, Jinks RN, Sougnez C, et al. Genetic mapping and exome sequencing identify variants associated with five novel diseases. PLoS One 2012;7:e28936.
[2] Saunders CJ, Miller NA, Soden SE, et al. Rapid whole-genome sequencing for genetic disease diagnosis in neonatal intensive care units. Sci Transl Med 2012;4:154ra135.
[3] Straussberg R, Ganelin-Cohen E, Goldberg-Stern H, et al. Lethal neonatal rigidity and multifocal seizure syndrome — report of another family with a BRAT1 mutation. Eur J Paediatr Neurol 2015;19:240–2.
[4] Saitsu H, Yamashita S, Tanaka Y, et al. Compound heterozygous BRAT1 mutations cause familial Ohtahara syndrome with hypertonia and microcephaly. J Hum Genet 2014;59:687–90.
[5] Hanes I, Kozenko M, Callen DJ. Lethal neonatal rigidity and multifocal seizure syndrome-a misnamed disorder? Pediatr Neurol 2015;53:535–40.
[6] Mundy SA, Krock BL, Mao R, Shen JJ. BRAT1-related disease-identification of a patient without early lethality. Am J Med Genet A 2016;170:699–702.