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BRAT1 GENE MUTATION PRESENTING AS REFRACTORY SEIZURES AND HYPERTONIA IN A NEONATE: A RARE CLINICAL ENTITY

Paediatrics

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ABSTRACT

Lethal Neonatal Rigidity and Multifocal Seizure Syndrome (RMFSL) is an uncommon and devastating epileptic encephalopathy caused by pathogenic mutations in the BRAT1 gene. This gene is essential for stabilizing the DNA damage response through its interaction with ATM and BRCA1 proteins. We present the case of a term male neonate with generalized hypertonia and refractory seizures from birth. Neuroimaging revealed basal ganglia gliosis and cerebellar hypoplasia. Whole exome sequencing confirmed a compound heterozygous mutation in exons 4 and 9 of the BRAT1 gene. Despite intensive support and multiple antiepileptic medications, the infant's condition rapidly deteriorated, consistent with the uniformly fatal nature of RMFSL. This report highlights the critical role of early genetic diagnosis in guiding prognosis and counseling in infants with neonatal epileptic encephalopathy.

KEYWORDS

INTRODUCTION:

Lethal Neonatal Rigidity and Multifocal Seizure Syndrome (RMFSL) is a rare, autosomal recessive condition marked by early-onset, treatment-resistant seizures and increased muscle tone. It was first reported by Puffenberger et al. in 2012, in Amish children with a frameshift mutation in the BRAT1 gene [1]. The BRAT1 gene (BRCA1-associated ATM activator 1) plays a central role in the DNA damage response pathway by regulating ATM (ataxia telangiectasia mutated) and BRCA1 proteins, which are vital for DNA repair [2].

Affected infants typically present with microcephaly, severe rigidity, refractory seizures, and early mortality-usually within six months. Given its rapid progression and poor prognosis, RMFSL represents a diagnostic challenge and necessitates a high index of suspicion for early genetic testing. To our best knowledge this is the first reported case of Indian origin. We reviewed all published cases of BRAT1 mutations reported in the English literature, along with the known functions of the BRAT1 gene, to gain insights into the disease's pathophysiology.

CASE REPORT:

A term male neonate was referred to our neonatal intensive care unit (NICU) on day one of life due to recurrent seizures and generalized hypertonia. He was born at 38 weeks of gestation via Emergency LSCS to non-consanguineous parents. His birth weight was 2.5 kg, and his head circumference measured 31 cm, placing him below the 3rd percentile, indicative of microcephaly. No significant antenatal complications were reported, and there was no family history of seizures, developmental delay, or neurological disorders.

On physical examination, the infant exhibited marked hypertonia of all four limbs, clenched fists, brisk deep tendon reflexes, and a small anterior fontanelle. Seizures were observed as generalized tonic-clonic activity involving all limbs, accompanied by twitching movements of the face and tongue. Neurological assessment revealed infant is encephalopathic with hypertonia of four limbs and brisk deep tendon reflexes.

Due to persistent seizures and respiratory compromise, the baby required mechanical ventilation for five days, following which he was gradually weaned and transitioned to continuous positive airway pressure (CPAP). Multiple antiepileptic drugs were initiated, including phenobarbitone, phenytoin, levetiracetam, and midazolam infusion, but the seizures remained refractory despite escalating doses.

A comprehensive diagnostic workup was performed. Blood cultures and sepsis screening were negative. Serum ammonia and lactate levels were within normal limits. TORCH workup was negative. Serum quantitative amino acids, urinary organic acids, acylcarinitines, total and free carnitine, lactate, and liver enzymes were normal. Electroencephalography (EEG) demonstrated mild diffuse cerebral dysfunction with prolonged inter-burst intervals. Brain MRI revealed basal ganglia gliosis, a simplified gyral pattern, and cerebellar hypoplasia, findings suggestive of underlying neurodevelopmental disorder.

Given the constellation of findings and treatment-resistant seizures, whole exome sequencing was performed, which identified compound heterozygous pathogenic variants in the BRAT1 gene involving exons 4 and 9, confirming the diagnosis of Lethal Neonatal Rigidity and Multifocal Seizure Syndrome (RMFSL). Despite maximal medical therapy and supportive care, the infant's condition continued to deteriorate, and he succumbed to cardiopulmonary arrest at 8 days of life.

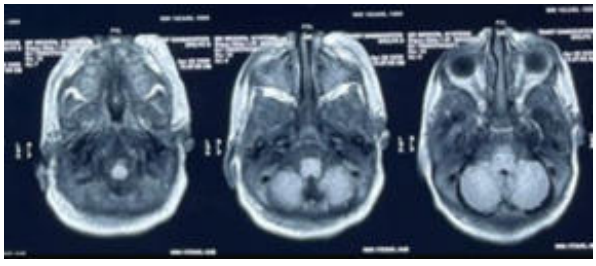

Figure-1 Cerebellarhypoplasia

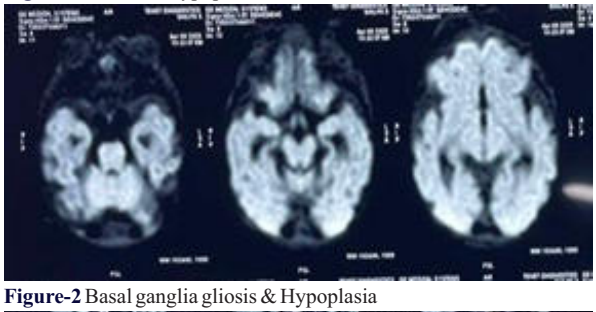

Figure-2 Basal ganglia gliosis & Hypoplasia

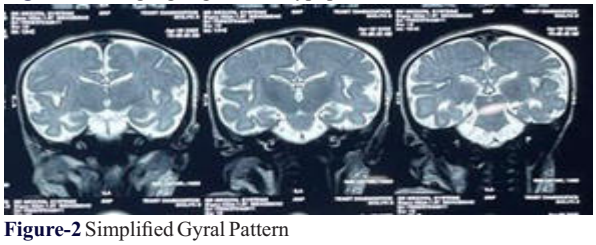

Figure-2 Simplified Gyral Pattern

DISCUSSION:

RMFSL represents a severe, early-onset epileptic encephalopathy

caused by BRAT1 mutations, leading to impaired DNA repair signaling pathways. The BRAT1 gene product is vital for stabilizing the activated ATM protein, which is essential for cellular responses to DNA damage. Mutations in BRAT1 disrupt this process, resulting in neurodevelopmental failure and early neurodegeneration.

Clinically, RMFSL manifests with intractable seizures, axial and limb rigidity, and microcephaly—findings that were consistent in our patient. Other reported features include small or absent fontanelles, overlapping sutures, and poor psychomotor development. EEGs often show multifocal discharges and background slowing. MRI findings may range from normal to cerebral and cerebellar hypoplasia, as seen in our case.

Treatment options are limited, and seizures are often refractory to conventional antiepileptic drugs and high-dose pyridoxine. Most affected infants develop respiratory failure and succumb within the first few months of life. Our patient deteriorated rapidly despite intensive supportive care and passed away on the 8th day of life.

Given the rapid progression and poor prognosis of RMFSL, early genetic testing should be considered in neonates presenting with unexplained seizures and rigidity. Including BRAT1 in targeted epilepsy gene panels can expedite diagnosis, enable genetic counseling for families, and inform decisions regarding supportive care.

CONCLUSION:

RMFSL is a rare but lethal neonatal epileptic encephalopathy caused by BRAT1 mutations. In neonates presenting with hypertonia, seizures from birth, and suggestive neuroimaging, early genetic testing should be pursued. Identification of BRAT1 mutations can confirm diagnosis, guide prognosis, and facilitate genetic counseling.

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