



## Clinical Observations

# Lethal Neonatal Rigidity and Multifocal Seizure Syndrome—A Misnamed Disorder?



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## ABSTRACT

**OBJECTIVE:** Lethal neonatal rigidity and multifocal seizure syndrome is a newly recognized genetic disorder associated with early onset of rigidity, multifocal epilepsy, developmental arrest, and early death. It is an autosomal recessive condition resulting from a mutation in the BRAT1 (BRCA1 [breast cancer-1]-associated ataxia telangiectasia mutated activator 1) gene. There are few cases in the literature, and all patients have died before age 2 years, most within the first 6 months of life. The objective of this report is to expand the phenotypic spectrum of BRAT1 disorders and propose new nomenclature for this condition. **RESULTS:** We describe a child with compound heterozygosity for mutations in BRAT1. Her neonatal course was unremarkable. Over the first year of life she was noted to have progressive global developmental delay, visual impairment, microcephaly, hypertonia, hyperreflexia, and seizures. No epileptiform discharges were seen on electroencephalogram. Serial magnetic resonance imaging of the brain showed progressive cerebellar and brainstem atrophy. Unlike previously described patients, our patient has gained a number of developmental skills and, at this time, is 3 years and 8 months old. **CONCLUSION:** Despite the name of this disorder, patients with lethal neonatal rigidity and multifocal seizure syndrome may not present until after the neonatal period and may have a much longer life span than previously reported. We suggest renaming the condition “BRAT1-associated neurodegenerative disorder” to avoid the assumptions associated with the original nomenclature and to encourage clinicians to consider this condition outside the neonatal period.

**Keywords:** lethal, neonatal, rigidity, seizure, microcephaly, BRAT1, genetic, encephalopathy

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## Introduction

Lethal neonatal rigidity and multifocal seizure syndrome is a severe epileptic encephalopathy characterized by the onset of rigidity and pharmacoresistant seizures at, or shortly after, birth.<sup>1,2</sup> The clinical features of this syndrome have been previously described in four case reports.<sup>1–4</sup> The consistent characteristics include pharmacoresistant seizures, arrested head growth, inability to swallow,

hypertonia, contractures, visual inattention, complete lack of developmental progress, and bouts of apnea and bradycardia leading to cardiac arrest and death.<sup>1,4</sup> In all previous reports, mutations in the BRAT1 (BRCA1 [breast cancer-1]-associated ataxia telangiectasia mutated [ATM] activator 1) gene were identified.<sup>1–4</sup> The affected infants did not achieve any developmental milestones, and almost all of them died within the first year of life.<sup>1–4</sup>

Here we describe a child with compound heterozygosity for mutations in BRAT1 whose clinical phenotype differs from those previously described. Unlike previously reported cases, this child did not come to medical attention until age 6 months, made developmental gains, and is still alive at almost 4 years of age, thereby raising concerns about the appropriateness of the name “lethal neonatal rigidity and multifocal seizure syndrome.”

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## Patient Description

This female infant was born at term to a nonconsanguineous Caucasian couple following an uncomplicated pregnancy. There were no concerns about decreased or abnormal fetal movements. She was delivered by emergency Cesarean section because of failure of labor progression and a nonreassuring fetal heart rate. She cried spontaneously and no resuscitation was required. Her Apgar scores were 9 and 9, at 1 and 5 minutes, respectively. Her birth weight was 3270 g (25th percentile), and her head circumference was 34 cm (50th percentile). At the time of delivery, she had good muscular tone and all primitive reflexes were present. No dysmorphic features were noted. The remainder of the newborn examination was normal.

Within the first month of life, she was described by her parents as “stiff” with “good head control.” By age 5 months, she had lost head control, although she continued to have increased appendicular tone. She was able to roll by age 9 months and sit with support by age 15 months. She never gained more advanced gross motor milestones. She held her hands fisted for the first 9 months but subsequently was able to grab and hold objects and transfer across midline. She never developed a pincer grasp. She developed humming and vocalizations by age 9 months but no babbling or words. She never consistently responded to her name or followed simple commands. She developed a social smile at age 9 months.

Concerns were first raised by the family at age 6 months. She then had poor visual fixation and following and excessive sleepiness. She was also noted to have plateauing of her head circumference (40.5 cm at 6 months, 10th percentile). Ophthalmologic assessment revealed poor pupillary responses bilaterally, poor fixation and following, and horizontal jerk nystagmus. Magnetic resonance imaging (MRI) of the brain and orbits at age 9 months was normal.

Her parents also raised concerns about “staring spells” occurring during feeding. These were first noted at age 3 months. At age 5 months, she had two episodes of brief eye rolling and unresponsiveness during feeding. Over the first year of life, these episodes became more frequent during feeding. A waking state electroencephalogram (EEG) at age 13 months was normal.

At the time of her first pediatric neurology assessment, the girl was 15 months old. She was referred by her pediatrician for possible seizures, global developmental delay, horizontal nystagmus, microcephaly, dysphagia, and an exaggerated startle response. On examination, her head circumference was 43 cm (less than 2nd percentile). She had no obvious dysmorphic facial features (Fig 1). Neurological examination was significant for slow roving eye movements with poor visual fixation and following along with gaze-evoked nystagmus. She also displayed axial hypotonia, appendicular hypertonia, and diffuse hyperreflexia with four beats of clonus at the ankles bilaterally. Further investigations at that point included levels of serum glucose, lactate, ammonia, urine ketones, venous blood gas, creatine kinase, thyroid stimulating hormone, serum copper, ceruloplasmin, alpha fetoprotein, serum amino acids, urine organic acids, urine purines/pyrimidines, and very-long-chain fatty acids and a chromosomal microarray analysis, all of which were normal. Given the occurrence of staring spells solely with feeding and the normal EEG, she was not administered an anticonvulsant.

Over the next 2 years, she gained few new developmental milestones but showed no regression. By age 2 years, a number of staring spells were captured on video and thought to be consistent with focal dyscognitive seizures, all lasting less than 30 seconds (see Video 1). No myoclonic seizures were noted. Her seizures increased in frequency with levetiracetam but improved with valproic acid. At age 2.5 years, she began to have episodes of pallor, hypothermia, and decreased responsiveness lasting minutes. These symptoms increased in frequency until they became daily. A number of events were captured on video EEG but were not associated with electrographic abnormalities (see Video 2).

Additional testing included 7-dehydroxycholesterol, isoelectric focusing of transferrin, acylcarnitines, urine sulfatides, urine mucopolysaccharide screen, cerebral spinal fluid neurotransmitter analysis, 48-hour Holter monitoring, and echocardiography, all of which were normal. The diagnosis of lethal neonatal rigidity and multifocal seizure syndrome was determined from results from a next-generation sequencing panel (Courtagen epiSEEK). Genetic abnormalities were found on each allele of the *BRAT1* gene. A maternally inherited frameshift change (c.294dupA), found to create a premature stop



**FIGURE 1.**

Images of the patient reviewed in this case report. (Left): at age 4 months. (Right): current photo. (The color version of this figure is available in the online edition.)

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