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Novel de novo Variants in the *BCL11A* and *RYR1* Genes in a Patient with Dias-Logan Syndrome and Elevated Creatine Kinase

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Abstract

Dias-Logan syndrome, also known as *BCL11A*-related intellectual disability, is caused by pathogenic variants in the *BCL11A* gene and yields a variety of signs and symptoms, including developmental delay, intellectual disability, microcephaly, and persistent fetal hemoglobin. The *RYR1* gene encodes the RyR1 protein of skeletal muscle and has been linked to increased susceptibility to malignant hyperthermia and various congenital myopathies. We describe the case of a 2-year-old male with mutations in both *BCL11A* and *RYR1* genes leading to an unusual presentation of Dias-Logan syndrome with global developmental delay, hypertonia, and elevated creatine kinase (CK). After extensive negative lab and genetic workups, the patient was diagnosed with the two mutations after undergoing whole-exome sequencing (WES). After his diagnosis, the patient received appropriate care and therapies to maximize his development and quality of life. The case describes an additional clinical picture of the rare Dias-Logan syndrome and a new potentially pathogenic variant in the *RYR1* gene. It also highlights the difficulties in diagnosing a patient with multiple gene defects and the importance of using WES in diagnosing neurodevelopmental disorders.

Keywords

Dias-Logan syndrome, *BCL11A, RYR1*, Developmental delay, Intellectual disability

Introduction

Dias-Logan syndrome, also known as *BCL11A*-related intellectual disability, is a genetic disorder caused by pathogenic mutations in the *BCL11A* gene characterized by intellectual disability, developmental delay, hypotonia, hypermobility, variable craniofacial anomalies, and elevated HbF levels [1,2]. It is extremely rare, with only 29 cases described in the literature thus far [3]. Mutations in the gene *RYR1* cause various congenital myopathies and an increased susceptibility to malignant hyperthermia [4]. We described the case of a 2-year-old male found to have novel de novo mutations in both the *BCL11A* and *RYR1* genes, leading to an unusual presentation of Dias-Logan syndrome and a complicated diagnosis. This case illustrates the difficulties of diagnosing someone with two simultaneous gene defects, provides an additional clinical description of the rare Dias-Logan syndrome, and describes a new, potentially pathogenic mutation in the *RYR1* gene.

Case Presentation

The patient is a 2-year-old male born to non-consanguineous parents of Mexican ethnicity. He was born at 38 weeks via spontaneous vaginal delivery at 6 pounds 12 ounces. There were no pregnancy complications or exposures during his gestation. The only neonatal complication he experienced was difficulty breastfeeding. His family history was insignificant for any developmental delay, seizure disorders, intellectual disability, or genetic disorders other than a paternal great-uncle who "looked syndromic and was delayed," according to the parents. No further information could be obtained about his paternal great-uncle.

He first presented to pediatric neurology with his parents at three months of age for microcephaly and episodes of arching

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his back. During later follow-up visits to pediatric neurology over the following two years, his microcephaly persisted, and he began to show signs of global developmental delay, including delays in gross and fine motor skills and speech. He started crawling at 14 months. He began pulling to stand and cruising at 26 months. He has had no regressions. He also began to have feeding difficulties and poor weight gain. In addition, his parents reported behavioral issues, including self-injurious behaviors (e.g., slapping himself in the head), constant rubbing of his eyes, rocking, and frequent screaming for no apparent reason. At this time, he had already started early intervention with physical therapy (PT), occupational therapy (OT), and speech therapy (ST).

On physical exam, the patient has dysmorphic craniofacial features, including hypertelorism, a broad nasal bridge, a philtrum with well-developed ridges, and large and everted ears. He has microcephaly with a head circumference of 44.7 cm (Z = -2.83) and short stature. He has alternating exotropia, bilateral hypermetropia, and generalized hypertonia. The patient's clinical features are compared to previously reported Dias-Logan syndrome patients in Table 1. He can walk across the room using a walker and stand for a maximum of 1 minute when wearing his orthotics; without his orthotics, he can only stand for a few seconds. He grabs toys with both hands and displays a raking grasp (no pincer grasp). He has a right-hand preference. He uses three words, including the Spanish equivalents of "mama" and "papa," and he mimics sounds. He does not follow commands and sometimes responds to his name.

Diagnoses considered included Fragile X, mitochondrial disorders, glycogen storage disorders, amino acid metabolism disorders, and other genetic causes of developmental delay and intellectual disability.

Prior negative workups included normal microarray, Fragile X, urine organic acids, plasma amino acids, urine creatine/GAA, carnitine/acylcarnitine profile, lactate, pyruvate, carbohydrate-deficient transferrin, and purine/pyrimidine panel. His electroencephalogram (EEG) and brain MRI with and without contrast were normal. The only consistent positive lab finding was elevated creatine kinase (CK), ranging from 281 to 548 U/L.

A Gene Dx microcephaly panel revealed four heterozygous variants of unknown significance (VUS) in four genes (*TUBGCP4*, *KNL1*, *CEP135*, *CENPF*) with known autosomal recessive conditions and was non-diagnostic.

After the family received genetic counseling, whole-exome sequencing (WES) was conducted on his DNA, including mitochondrial DNA. It revealed a novel de novo heterozygous pathogenic variant c.1411A>T (p.Lys471Ter) in the *BCL11A* gene, consistent with a diagnosis of Dias-Logan syndrome. Additionally, he was found to be heterozygous for a novel de novo VUS c.5198A > T (p.Glu1732Asp) in *RYR1*.

While there is no cure or specific treatment for Dias-Logan syndrome, the patient continued ST, OT, and PT. He was also referred to a local pediatric extended-care daycare center for skilled nursing and care tailored to children with medical conditions. He was previously denied daycare at this specialized center, but his new genetic diagnosis allowed him access to this resource. In addition, he was referred to a center for child development and behavioral health for an evaluation of autism spectrum disorder and additional therapies to help with his behavior and development problems. He also began seeing a nutritionist to aid his eating behaviors and weight gain.

The patient's family continues to utilize ST, OT, and PT to aid the patient's development. He has shown considerable progress, especially in his motor skills. The multidisciplinary approach to his care will help maximize his developmental capabilities and increase his and his family's quality of life.

Table 1: Clinical features of the patient in this case report compared to previously reported Dias-Logan syndrome patients.

Clinical features	Eleven patients described by Dias, et al. [1]	The patient in this case report
Abnormal external ears	5/8	+
Autism spectrum disorder	3/10	Likely
Behavior problems	6/9	+
Blue sclerae in infancy	4/8	-
Down-slanting palpebral fissures	4/8	-
Everted lower face	6/8	-
Flat midface	6/8	-
Global developmental delay/intellectual disability	10/10	+
Joint hypermobility	7/8	-
Language delay	10/10	+
Microcephaly	5/9	+
Strabismus	8/8	+
Thin upper lip	7/8	-

Legend: + represents the presence of clinical feature; - represents the absence of clinical feature; "likely" means the patient displays many signs of autism, but an official evaluation has not yet been completed

In addition, with consent from both parents, the patient's family was connected to another known family with a child with a *BCL11A* mutation. Little is known about the long-term prognosis of Dias-Logan syndrome, but there does not seem to be any regression of skills with the disorder [2]. The life span and typical cause of death in these patients are unknown due to the small number of individuals with this disorder who have been described in the literature; however, there are reported cases of individuals aged 19 and 23 who are alive and well, showing that survival into adulthood is possible [2]. The patient's family was educated on the potential pathogenicity of his VUS in the *RYR1* gene and to remain vigilant of any signs and symptoms signaling a myopathy. They were also educated on his potential susceptibility to malignant hyperthermia, and this was added to his chart in case of any future need for anesthesia.

Discussion

The *BCL11A* gene encodes a regulatory C2H2 zinc-finger protein essential during tissue development, especially in the hematopoietic and neurologic systems [1]. The murine form of this gene, *bcl11a,* has been shown to play crucial roles in neurite arborization and the development of neural networks [5]. Dysfunction in neurite arborization and neural network building may lead to neurological dysfunction in those with BCL11A loss-of-function mutations. It also plays a significant role in the hematopoietic system, where it silences HbF; this is why those with loss-of-function mutations in *BCL11A* have elevated levels of HbF [1].

The *RYR1* gene encodes the type 1 ryanodine receptor channel (RyR1), a calcium channel with essential functions in excitation-contraction in human skeletal muscle [4]. Mutations in *RYR1* are known to cause numerous congenital myopathies, including central core disease (CDC), core-rod myopathy, centronuclear myopathy (CNM), congenital fiber-type disproportion (CFTD), and multi-minicore disease (MmD), genetic myopathies that cause various histopathological findings and clinical myopathic symptoms. *RYR1* is also implicated as one of the significant genes in which mutations cause an increased susceptibility to malignant hyperthermia [4].

While the *BCL11A* mutation explains most of the patient's signs and symptoms, the hypertonia and elevated CK levels do not fit the clinical picture of previously described cases of Dias-Logan syndrome. His elevated CK and generalized hypertonia are likely due to the additional mutation in the *RYR1* gene. Previously described cases report hypotonia as a significant finding but not hypertonia [6]. It is unclear whether his heterozygous *RYR1* variant is pathogenic, as it has not been described in the literature. This case shows how difficult diagnosing a rare disease can be, especially when one patient has multiple gene defects, which can lead to a blurry clinical picture. This case depicts how important WES can be to the diagnosis of neurodevelopmental disabilities, especially in those whose initial labs and preliminary genetic workup are non-diagnostic. This allows early intervention and tailored healthcare to the patient to maximize their development. It also decreases unnecessary and costly diagnostic workups and gives caregivers peace of mind about what to expect with their child's development and future.

This case's strengths include our patient's descriptive clinical picture, which helps describe a rare disorder with relatively few cases described worldwide. One of our case's weaknesses is the inability to determine whether the patient's hypertonia and elevated CK represent unusual presentations of Dias-Logan syndrome or effects from his additional *RYR1* gene mutation. Only time will tell whether or not his *RYR1* gene mutation represents a true pathogenic mutation with latent onset of myopathy.

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