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Newborn with *Arthrogryposis multiplex congenita*: A novel TOR1A gene mutation

Santo Di Marco; Daniela Doni*; Gaia Kullmann; Maria Iascone; Eugenia Mariani; Rosita Menichini; Alessandro Molinaro; Veronica Ferro; Tiziana Fedeli; Maria Luisa Ventura

***Corresponding Author: Daniela Doni**
Department of Neonatal Intensive Care Unit, FMBBM, San Gerardo Hospital, Monza, Italy.
Email: danieladoni9@gmail.com

Abstract

Arthrogryposis Multiplex Congenita (AMC) is characterized by congenital, non-progressive, and symmetric joint contractures that involve at least two different body areas. AMC is a heterogeneous disease. Arthrogryposis Multiplex Congenita-5 (AMC5) caused by biallelic *TOR1A* gene mutations (the gene encodes for Torsin-1A, a member of the AAA family of adenosine triphosphatases). Here, we present a case of a female newborn with frontal hypertrichosis, deep-set eyes, hypomimic facies, no spontaneous motility, bilateral severe hip dysplasia, arthrogryposis of elbows, knees, and feet (congenital clubfeet). Genetic testing detected novel TOR1A mutation (p.Asp264Ilefs*13 variant).

Keywords

Arthrogryposis multiplex congenital; AMC; TOR1A; DYT1.

Introduction

The *TOR1A* gene encodes for Torsin-1A, a member of the AAA family of Adenosine Tri phosphatases (ATPases). This protein participates in several cellular activities, including protein chaperone activities, membrane trafficking, organelle biogenesis and powering cellular proteins [1]. The *TOR1A* mutations behave as dominant or recessive, which account for generalized early onset dystonia and for the more severe phenotype of congenital arthrogryposis.

Arthrogryposis Multiplex Congenita (AMC) is characterized by congenital, non-progressive, and symmetric joint contractures that involve at least two different body areas. The incidence is approximately 1 in 3000 to 5000 live births [2].

AMC is a heterogeneous disease, and hundreds of conditions with arthrogryposis have been reco-

gnized with different etiologies.

One of these conditions is Arthrogryposis Multiplex Congenita-5 (AMC5) caused by biallelic TOR1A gene mutations. Patients affected by AMC5 showed severe contractures of large and small joints, congenital hip dislocation, strabismus, developmental delay and intellectual disability. The patients had poor overall growth, and some had dysmorphic features, such as prominent occiput, deep-set eyes, ptosis, upslanting palpebral fissures, short upturned nose, large, low-set and posteriorly rotated ears, retrognathia, wide mouth, high-arched palate, and short neck [2].

Mutations in TOR1A gene can manifest others different phenotypes such as DYT1 dystonia, a rare autosomal dominant condition with incomplete penetrance, caused by an in-frame GAG deletion (p.Glu303del) in the endoplasmic reticulum luminal protein torsin A encoded by TOR1A (9q34.11) [3]. These patients show dystonic movements characterized by repetitive and sustained involuntary muscle contractions resulting in severe twisting movements and abnormal postures involving one or more sites of the body. Severity of symptoms and distribution vary widely between affected individuals.

Case Report

We present a case of a female newborn with novel TOR1A mutation. She was first child of a consanguineous couple (first grade cousins), born at 36 weeks of gestational age by caesarian section. Her birth weight was 2,350 g (12^{th} percentile), length 40 cm (0^{th} percentile), and head circumference was 32,5 cm (49^{th} centile). The APGAR scores were 4 and 7 at 1 and 5 minutes respectively.

The pregnancy was complicated by intrauterine growth restriction, reduced fetal movements, arthrogryposis and polyhydramnios. Invasive prenatal genetic tests were performed on amniocentesis. CGH Array, and cariogram were normal, no teratogenic exposures or maternal illnesses were reported.

No relevant family history, specifically no history of arthrogryposis or dystonia;

At birth the patient required endotracheal intubation and stayed at the Neonatal intensive care unit for the first 4 months of life, due to respiratory distress syndrome and a cardio-respiratory arrest occurred at 89 days of life, requiring cardiopulmonary resuscitation.

Physical examination at birth reveals, frontal hypertrichosis, deep-set eyes, hypomimic facies, no spontaneous motility, bilateral severe hip dysplasia, arthrogryposis of elbows, knees, and feet (congenital clubfeet). She needed constant aspiration of secretion as she showed sialorrhea and dysphagia. The patient showed dystonic movements and generalized muscolar rigidity, in particular of the thoracic muscles, conditioning respiratory distress, which required treatment with benzodiazepines and muscle relaxants. Her EEG was normal and cerebral MRI performed at 30 days of life showed large periencephalic liquor spaces and thin spinal cord in the mid-upper dorsal tract. Echocardiography and oculistic evaluation were performed and resulted normal.

Trio-whole exome sequencing was performed. Indeed, after genetic counseling and written infor-

med consent, genomic DNAs of the patient and both parents were extracted using standard procedures. The exonic regions and flanking splice junctions of the genome were captured using the Clinical Research Exome v.2 kit (Agilent Technologies, Santa Clara, CA). Sequencing was done on a NextSeq500 Illumina system with 150bp paired-end reads. Reads were aligned to human genome build GRCh37/UCSC hg19, and analyzed for sequence variants using a custom-developed analysis tool [4]. Additional sequencing technology and variant interpretation protocol have been previously described [4]. Coverage on target for the prob and was ≥10x for 98% with a mean coverage of 238x.

The trio-WES analysis identified a homozygous four-bases deletion located in exon 5 of the TOR1A gene (NM_000113.3:c.790_793). The variation generates a 'frameshift' as a coding effect, starting at codon Asp264. The new reading frame ends in a stop codon at position 13 (p.Asp264Ilefs*13). Both parents were found to be healthy heterozygous carriers. The deletion occurred in the last exon of the TOR1A gene and is predicted to produce a protein shorter than 56 amino acids that could be responsible for the clinical features. The novel variant was classified as likely pathogenic according to ACMG Guidelines [5]. Upon discharge the patient continued palliative treatments in a specialized center. She died at the age of 7 months.

Discussion

The protein coded by TOR1A, torsinA, contains 332 amino acids and is widely expressed in the endo-plasmic reticulum and is thought to function as an adenosine triphosphate-regulated chaperone in the secretory pathway and the nuclear envelope. Mutation of this protein are related with DYT1 (early-onset primary dystonia), caused by an in-frame GAG nucleotide deletion in the TOR1A gene [3,6].

Overall, published research supports that DYT1 is caused by the loss of torsinA function, likely due to a dominant negative effect of the mutant torsinA over the wild-type protein [7]. Animal models of DYT1 have been developed and demonstrate that torsinA is essential for postnatal life, mutated mice die within 48 hours of birth [8].

Of interest, the animal models described above appear normal at birth except for a smaller size than their littermates, however, do not feed or generate sounds, suggesting oropharyngeal dysfunction. Gross neuroanatomy is normal, but they have ultra structural defects in neurons. Mice with restricted conditional deletion of torsinA exhibit longer survival [9]. Our patient exhibits several features observed in animal models, including oropharyngeal dysfunction and delayed growth with no gross neuroanatomical defects appreciated by MRI.

The p.Asp264Ilefs*13 variant has not been previously associated with the disease. Still, it is expected to result in a translational frame shift at the residue 264, deleting the terminal part of the typical protein. Nevertheless, given the current knowledge, it is reasonable to speculate that this mutation in homozygosis results in the severe congenital phenotype observed.

In conclusion, the case presented here further demonstrates how TOR1A mutations can cause different phenotypes in dominant or recessive forms [10]. An open question is how the impairment of the same

gene can explain these distinct phenotypes.

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Authors Information: Santo Di Marco[1]; Daniela Doni[2]*; Gaia Kullmann[3]; Maria Iascone[4]; Eugenia Mariani[1]; Rosita Menichini[1]; Alessandro Molinaro[1]; Veronica Ferro[3]; Tiziana Fedeli[2]; Maria Luisa Ventura[2]

[1]Department of Pediatrics, Università degli Studi Milano Bicocca, Milano, Italy.

[2]Department of Neonatal Intensive Care Unit, FMBBM, San Gerardo Hospital, Monza, Italy.

[3]Department of Neuropsychiatry, San Gerardo Hospital, Monza, Italy.

[4]Medical Genetic Department, ASST Papa Giovanni XXIII, Bergamo Italy.

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