International Journal of Medicine & Healthcare
Vol. 6, No. 1, 2021, pp. 51-58
http://ijmh.ielas.org/index.php/ijmh
ISSN: 2545-4188 (online)

https://doi.org/10.5281/zenodo.5098370

LAMA2–ASSOCIATED CONGENITAL MUSCULAR DYSTROPHY: CASE REPORT

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Received: 2021-05-31 **Accepted:** 2021-06-30 **Published online:** 2021-07-14

Abstract

Introduction: LAMA2 Associated Muscular Dystrophy (LAMA2-RD) is one of the most common forms of congenital muscular dystrophy worldwide. Mutations in the LAMA2 gene affect the production of the α2 subunit of lamin-211 (merosine) and result in partial or complete deficiency of lamin-211. Inheritance is usually autosomal recessive.

Case report: We present a patient who is dual heterozygous for two pathogenic variants in the LAMA2 gene, as demonstrated by targeted resection of 4800 clinically significant genes. c.4474dupT, p. (Tyr1492LeufsTer11), inherited from the mother and c.7732C> T, p. (Arg2578Ter), inherited from the father. With this genotype the patient is confirmed autosomal recessive disease, LAMA2-RD. Variant c.4474dupT, p. (Tyr1492LeufsTer11), in exon 31 of the LAMA2 gene, is a change that has not been reported in the literature.

Conclusion: Genetic confirmation of the diagnosis is important for genetic counseling, prenatal diagnosis for each subsequent pregnancy in the family because the risk of an affected child is 25%.

Keywords: LAMA2 associated muscular dystrophy, genetic testing of clinically relevant genes, genetic counseling.

1. Introduction

Mutations in the LAMA2 gene affect the production of the α2 subunit of lamin-211 (merosine) and result in partial or complete deficiency of lamin-211 (Turner, et al., 2015). Complete and partial merozine deficiency is called LAMA2 associated muscular dystrophy (LAMA2-RD) and is one of the most common forms of congenital muscular dystrophy worldwide. LAMA2-RD is a disorder that causes weakness and wear (atrophy)

of the muscles used to move (skeletal muscle). This condition varies in severity of the clinical picture, from severe type with early onset to mild form with late onset. Complete merosine deficiency is associated with a more severe form of congenital muscular dystrophy (CMD), which is clinically manifested by hypotonia and weakness at birth, development of large joint contractures, and progressive respiratory involvement. Muscle atrophy and severe weakness disable independent movement. Partial merosine deficiency is manifested by limb weakness and joint contractures, so that independent movement is usually achieved (Sarkozy, et al., 2020).

LAMA2-RD is characterized by changes in both the central and peripheral nervous systems with abnormal white matter magnetic resonance imaging of the brain MRI of the brain and dystrophic muscle as evidenced by muscle biopsy, as well as creatine kinase (CK) levels which are usually increase to> 1,000 IU / L. The use of the new generation sequencing (NGS) significantly improves the diagnostic capabilities of LAMA2-RD. The majority of patients with merosine deficiency carry recessive pathogens in the LAMA2 gene.

The early form of LAMA2-RD is seen at birth or in the first few months of life. It is part of a group of muscle disorders called congenital muscular dystrophies and is sometimes referred to as congenital muscular dystrophy type 1A. About 2/3 of patients have symptoms at birth, and 1/3 of the symptoms are recognized during the first 6 months of life (Geranmayeh & al, 2010; Xiong & al, 2015).

Newborns may have severe muscle weakness, lack of muscle tone (hypotonia), poor spontaneous movements, and joint deformities (contractures). Weakness of the muscles of the face and throat can result in difficulty eating and inability to grow and gain weight at the expected rate(Bertini, et al., 2011). Respiratory failure, which occurs when the chest muscles are weakened, causes poor crying and breathing problems that can lead to frequent, potentially life-threatening lung infections. These children often develop spinal deformities, scoliosis, and lordosis, and are often unable to walk on their own. Speech difficulties may occur. Seizures occur in about one-third of children with early LAMA2-RD, and heart complications are rare (Natera-de Benito, 2020; Marques, 2014).

The late form of LAMA2-RD occurs later in childhood and belongs to a group of muscle disorders classified as muscular dystrophies in the extremities, the most affected are the muscles closest to the body (proximal muscles), specifically the muscles of the shoulders, upper arms, pelvic area and thighs. These children have delayed development of motor skills, such as walking, but generally achieve the ability to walk without assistance. Over time, they may develop scoliosis of the back, joint contractures, progressive respiratory failure, and cardiomyopathy. However, most affected people retain the ability to walk and climb stairs.

Scientific studies show that there is a risk of developing malignant hyperthermia during anesthesia. (Shukry, et al., 2006; Scrivener, et al., 2014).

Different incidence and mortality rates have been reported in the literature depending on the type of CMD and population studies. The average CMD frequency is 1-9 per 100,000, ranging from 1 in 125,000 in Italy to 1 in 16,000 in Sweden. The most common form worldwide is considered to be muscular dystrophy with merozin type 1A deficiency, called MDC1A (due to lamin-α2 defects), accounting for 30-40% of all CMD cases (Dimova & Kremensky, 2018).

The diagnosis of CMD requires a thorough clinical assessment, a detailed history of the patient, identification of characteristic symptoms, and various specialized tests, including biopsy of the affected muscle tissue, which may reveal characteristic changes in muscle fibers, electromyography, and specialized blood tests, immunohistochemistry, magnetic resonance imaging (MRI) and molecular genetic testing.

Abnormal white matter signals (in almost all individuals with LAMA2-RD) have been reported on FLAIR MRI, including the T2 sequence hypersignal and the T1 sequence hyposignal in areas of ongoing myelination (i.e., subcortical and periventricular areas), sparing areas whose myelination is later in life (i.e. corpus callosum and inner capsule) (Geranmayeh & al, 2010). Two siblings with a late-onset phenotype have been reported to have near-normal brain magnetic resonance imaging (Saredi & al, 2019).

Other but rarer LAMA2-RD-associated MRI findings are structural abnormalities in the brain (secondary to neuronal migration defects), which include cortical dysplasia (Mercuri & al, 1999), lysencephaly (agiria or pachigiria) (Jayakody, 2020; Muaremoska Kanzoska, 2019), and polymicrogyria(Vigliano, et al., 2009). They are more often associated with epilepsy.

The diagnosis of LAMA2-RD is made by molecular genetic testing and the identification of suggestive findings or bialelic (homozygous or double heterozygosity) pathogenic variants in LAMA2. Molecular genetic testing approaches may include a combination of genetically engineered testing (single gene testing, different multigene panels) and comprehensive genomic testing (exome sequencing, exom sequence, chromosomal micro-array (CMA), sequence order of the phenotype.

Gene-directed testing is likely to be used to diagnose individuals with a typical phenotype (familial burden with the disease), while those with a later onset or atypical phenotype who do not consider the diagnosis of LAMA2 muscular dystrophy are more likely to are diagnosed using a larger multigene panel or even comprehensive genomic testing (Oliveira & al, 2020).

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2. Case Report

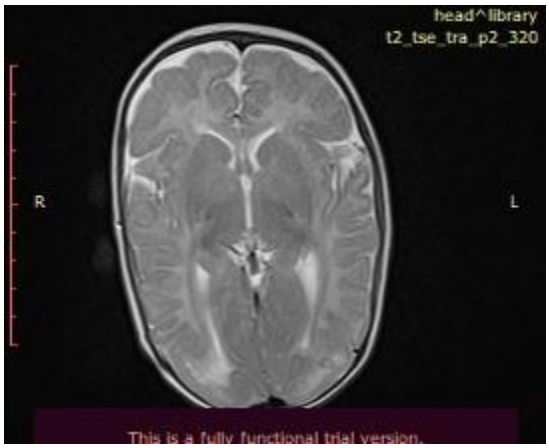
We report a male child, from the third regular and properly controlled pregnancy. First live child. The first, a female child, died at the age of 10 days. The second pregnancy ended in miscarriage in the second month of pregnancy. The child was born in 40 GW, spontaneously with the head presentation, with BW = 3140 gr; BL = 53 cm. APGAR 8/9. No data of interest for the perinatal and early postnatal period.

The first examination at the University Clinic for Children's Diseases in the neurological-developmental ambulance was made at the age of 3 months, due to developmental delay and the appearance of deformities of the hands and feet.

The neurological examination revealed marked hypotonia of the body axis, inability to cause age-characteristic primitive reflexes, attenuated tendon reflexes and contractures of the hands and feet.

A multidisciplinary approach and extensive laboratory processing have been implemented. From the obtained results for marking are the following: AST = 147 U/l; ALT = 84 U/l; LDH = 620 U/L; GGT = 20 U/L; CK = 5329 U/L.

Magnetic resonance imaging of the brain was performed according to standard pulse sequences and directions. From the displayed examination, irregular hypersignal zones can be seen bilaterally occipitally behind the posterior horn of the lateral ventricles, where the change is more pronounced on the right side. The same in the T1 pulse sequence shows hyposignal intensity. The ventricular system and subarachnoid spaces are within normal limits.



Pic.1 Magnetic Resonance

On Electromyography (EMG) - spontaneous activity is not registered. When trying to contract the muscles of the examined muscles, no reduction of the track is registered, AMP is predominantly of low amplitude. The motor conduction is immeasurable on the whole lower leg due to the inability to register an M wave from the most distal muscles (small muscles at that age), but from the calf muscles (m. Tib. I m. Quadriceps fem. Lat. Sin) low-voltage M waves are obtained with neat latencies for age (unfinished myelination). This finding suggests that the motor unit is affected due to damage to the muscle fibers themselves.

Suspected primary muscle disease - congenital muscular dystrophy and given advice for continuous physical therapy.

The patient appears for re-examination at 2 years and 8 months age. Neurological status showed marked hypotonia of the body axis, areflexia, present contractures in the distal joints, and scoliotic altered spine.

Developmental tests have been performed and they show the most severe lag in the development of large motor skills, it corresponds to the age of 2 months, the development of speech and mental capacities showed a slight lag, that is at the age of 19 months.

Targeted sequencing of 4800 clinically significant genes has been performed. The patient is a double heterozygote for two pathogenic variants in the LAMA2 gene: c.4474dupT, p. (Tyr1492LeufsTer11), inherited from the mother, and c.7732C> T, p. (Arg2578Ter), inherited from the father. With this genotype the patient is confirmed autosomal recessive disease, LAMA2-RD.

3. Discussion

The LAMA-2 gene is located on chromosome 6 and encodes the alpha-2 subunit of the lamina protein 2. Proteins belonging to the lamina group are located in the extracellular matrix and are involved in the regulation of cell growth, motility, and adhesion to other cells. Lamin 2 protein is expressed in muscle and nerve cells and plays a role in maintaining skeletal muscle stability. Pathogenic changes in the LAMA2 gene are responsible for LAMA2-associated muscular dystrophy with an autosomal recessive inheritance.

The prognosis of clinical severity depends on several variables, including age at onset, the LAMA2 pathogenic variant, and, if known, the effect of the variant on protein function (Geranmayeh & al, 2010; Oliveira & al, 2018).

The complete absence of α2 lamin and the phenotype of congenital muscular dystrophy type 1A (MDC1A) are generally caused by loss of function of the LAMA2 variants (Pegoraro & al, 1998; Oliveira & al, 2018); however, exceptions occur,

including homozygotes for pathogenic nonsense LAMA2 variant, which individuals who have achieved independence (Geranmayeh & al, 2010).

Phenotypes associated with partial α2 lamin deficiency tend to be less severe, with slower disease progression (Allamand & Guicheney, 2002; Tezak & al, 2003; Oliveira & al, 2018). Some missense, splice site, in-frame variants are associated with partial deficiency, as well as pathogenic n variants of failure in canned cysteine residues of the laminar α2 protein LAMA2-MD with a late onset has been observed in many individuals with variant c. 2461A> C (p.Thr821Pro) in homozygosity or compound heterozygosity with another variant (Oliveira & al, 2018).

The following pathogenic variants have been found in our patient: The variant c.4474dupT, p. at position 1492 with the amino acid lysine and termination of the protein after 11 amino acids. This change has not been published in the literature so far.

Variant c.4474dupT is classified as pathogenic according to the following ACMG (American College of Medical Genetics and Genomics) criteria (PMID: 25741868).

- PVS1: Truncation variant in the LAMA2 gene where a number of frameshift variants are classified as pathogens
- PM2: The variant is not found in the gnom AD database
- PM3: The variant occurs in a trans position with another pathogenic variant in LAMA2 genot c.7732C> T, p. (Arg2578Ter) in the affected patient.

The variant c.7732C> T, p. (Arg2578Ter) in exon 55 of the LAMA2 gene is a nonsense variant that changes the amino acid arginine into a terminal codon and thus shortens the amino acid sequence of the protein to position 2578. This variant is known in published several times in the ClinVar database (rs121913572) as a pathogenic variant in individuals with hereditary muscular dystrophy (PMID: 24611677, PMID: 20207543, PMID: 12601554).

Family studies have shown that variant c.4474dupT, p. (Tyr1492LeufsTer11) in the LAMA2 gene is present in the heterozygous mother, while variant c.7732C> T, p. (Arg2578Ter) in the LAMA2 gene is present in the heterozygous father.

Genetic counseling is recommended, prenatal diagnosis for each subsequent pregnancy in the family because the risk for an affected child is 25%. Cascading testing is recommended to determine the bearing of detected defects in other family members.

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