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# A Novel De Novo Mutation In Lamin A/C Gene In Emery Dreifuss Muscular Dystrophy Patient With Atrial Paralysis

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**Abstract**

We present a 26 year old female Indonesian patient with full spectrum Emery Dreifuss Muscular Dystrophy (EDMD) characterized with contracture of elbows, heel cord and pelvic muscle wasting and weakness and atrial paralysis, as rare cardiac findings in EDMD . A novel de novo pathogenic heterozygous missense mutation (NM_170707.3: c.122G>T, p.Arg41Leu) in exon 1 was detected. Preventing atrial paralytic patients from systemic embolism is important. Early diagnosis, intervention, targeted management and counseling are necessary for a better health and life quality of individuals with EDMD.

## Introduction

Emery Dreifuss Muscular Dystrophy (EDMD) is a rare genetic disorder, characterized by early contractures, slowly progressive muscle wasting and variable cardiac conduction defects. The disease was firstly describe as X-linked muscular dystrophy, but later autosomal dominant and autosomal recessive forms were reported.[1]-[4] Lamin A/C (LMNA) gene on 1q21.2-q21.3 is responsible for autosomal-dominant form of EDMD. Mutation in this gene played role in skeletal and cardiac muscular defects.[2]-[3] In the past three decades, atrial standstill phenotype is rarely reported to develop in all forms of EDMD inheritance.[5]-[8]

## Case Report

We present a 26 year old female patient with some episodes of presyncopal states and contracture of elbows, knees, heels with muscle wasting. At age 7, she was seen to have mild contracture of knees and heels. When she was 12, she required wheelchair to travel distances greater than 10 meters. The first cardiac abnormality was noted at the age 18. She presented to the physician due to palpitation. Holter monitoring showed low amplitude P waves and first degree AV-block with ventricle premature complex.

Recent physical examination, contracture of elbows, knees and heels are obviously seen [Figure 1a] and [Figure 1b]. High level of creatinin kinase was found (709 U, normal < 167 IU). Electrocardiography (ECG) showed conduction abnormality (absence of P-waves) as depicted in [Figure 2]. Transthoracic echocardiography showed atrial enlargement and no 'A' wave in the Doppler mitral flow pattern correspond to atrial mechanical standstill. The diagnosis of atrial paralysis was further supported when we found no atrial electrical activity in the right atrial appendage, interatrial septum and lower right atrial during DDDR implantation procedure. The ventricle was easily paced with 0.5mA and the mode was changed into single ventricle pacing system (VVIR). Six month after PPM implantation she was admitted to another hospital due to embolic stroke.

No other family members were reported to be affected with the same abnormalities. Based on the clinical features, Sporadic Autosomal Dominant form of EDMD was suspected. Therefore, molecular analysis of the LMNA gene was warranted. Sanger sequencing of all coding exons and surrounding splice sites of the LMNA gene was performed as described below. The genomic DNA reference sequence was NM_170707.3. PCR of exon one was performed using primers ACTCCGAGCAGTCTCTGTCC (forward) and GCCCTCTCACTCCCTTCC (reverse). One hundred nanograms of DNA solution (1 µL) were added into PCR mixture, which contained 12.5 µL ReadyMix formulation (2x) of KAPA2G Fast PCR master mix (KAPA Biosystems), 1 µL of primers working solution, and 10 µL of $H_2O$. Amplification was performed using PCR System 9700 (Applied Biosystem) with the following protocol. PCR was initiated by 10′ denaturation at 95°C, followed by 35 PCR cycles (30" 95°C, 30" 60°C, 60" 72°C) and 7′ final elongation at 72°C. Sequence result was compared to published reference sequence using Mutation Surveyor software version 5.0 (Applied Biosystems Genetic Analyzers, MegaBACE, and Beckman CEQ electrophoresis systems). In exon one, a missense mutation has been detected, changing a CGC codon (coding for arginine) into a CTC (coding for leucine); c.122G>T, (p.Arg41Leu)) (nomenclature according to the

**Key Words**

Emery-Dreifuss Muscular Dystrophy, Atrial Paralysis, Mutation Lamin A/Cl.

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HGVS guidelines; http://www.hgvs.org/mutnomen/) [Figure 3]. To our knowledge, this mutation has not been reported before. Carrier testing with the same protocol as mentioned above were performed and revealed that the mutation had occurred de novo.

## Discussion

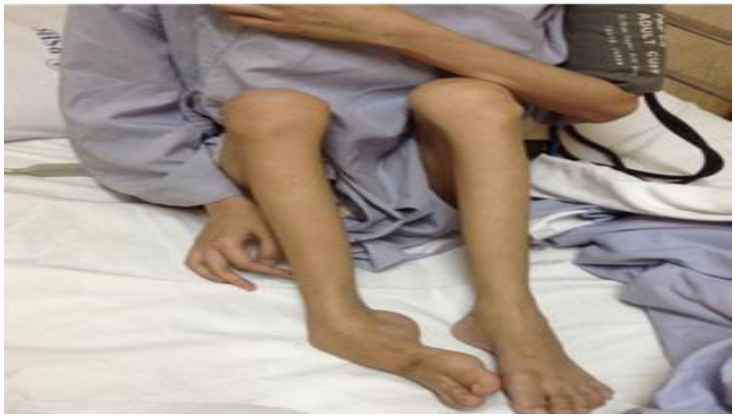

**Figure 1a:** Patient shows muscle wasting and contracture of knees and heels.

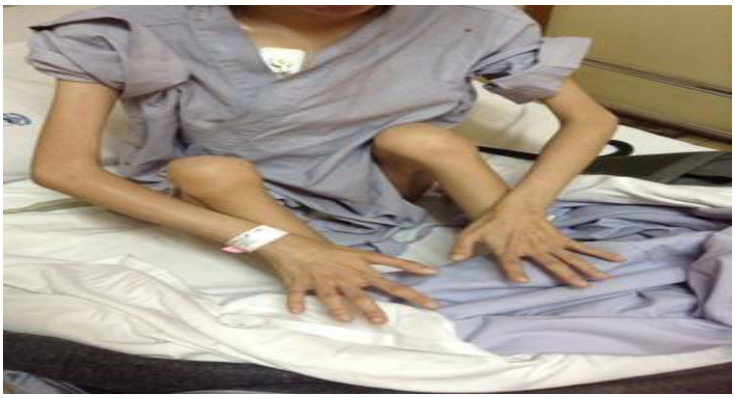

**Figure 1b:** Patient shows contracture of elbows.

Most clinical features of our patient, who had contracture of elbows, heel cord, pelvic, muscle wasting and weakness and cardiac junctional rhythm, are consistent with those described in the EDMD literature.[1]-[3] In addition, our patient showed atrial paralysis that is rarely reported to develop in EDMD. In the past three decades, only five EDMD patients including our case were reported to develop atrial paralysis (see [Table 1]).[5]-[8]

Lamin A/C gene consists of 12 exons that produce at least four types of RNA via alternate splicing including lamins A,A**δ**10, C and C2. Lamin A and C are intermediate filament proteins that form a helical dimer through their rod domains. Lamin A and C differ in the length and aminoacid sequence of their carboxyl terminals, but the initial 566 aminoacids (5' and rod domain) of both lamins are identical. The lamin A/C protein is expressed in the nuclear envelope of many tissues, primarily in skeletal and cardiac muscle.[9] The mutations in this gene lead to several laminopathies through

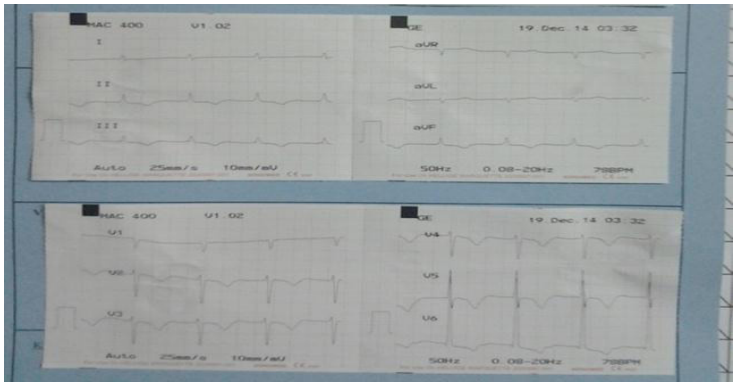

**Figure 2:** Electrocardiogram showed persistent junctional bardycardia rhythm (absence of P-waves).

defects in mechanical integrity of cells, alteration in regulation of tissue-selective transcription, and defect in cell proliferation.[9]-[10]

Atrial paralysis is histopathologically described as replacement of normal atrial muscle with non-functional fibrous tissue.[11] Regarding LMNA function, this cellular change was hypothesized as a result of structural changes in nuclear envelope due to mutated lamin that leads to decreased nuclear stability and impaired nuclear-cytoskeletal coupling. This condition results in a higher susceptibility to nuclear rupture and cardiomyocyte apoptosis and will likely to be replaced by fibrosis in later stages of the disease. This may provide a possible substrate for conduction block and re-entrant arrhythmias.[12],[13]

So far, 24 mutations in the Lamin A/C gene have been reported.[3]-[5],[12],[14]-[18] The particular mutation detected in our patient (c.122G>T, (p.Arg41Leu)) has not been reported before. This mutation is located in **α**-helical central rod domain of lamin A and C protein structure [Figure 4]. Felice et al suggested that mutation in the rod domain of the lamin A/C gene may cause the full clinical spectrum of EDMD-AD which comparable to our patient.[18] However, Fatkin et al suggested that missense mutation in the tail region of Lamin A and C cause EDMD while rod mutations cause isolated myocardial disease.[14] Atrial paralysis is less documented in the literature. Tabel 1 shows the comparison between atrial paralysis patients with different mutations. The development of atrial paralysis starts in the late late third to fourth decade in all of age in all patients. We are trying to

**Table 1:** Summary of clinical features and genomic study in EDMD patients with atrial paralysis

| Patient | Age | Sex | Muscular findings | Cardiac findings | Inheritance | Genetic study | Reference |
|---|---|---|---|---|---|---|---|
| 1 | 29 | Male | Severe skeletal dystrophy (Contracture of elbows,hips, rigid spine, wide spread muscular hypotrphy) | Atrial paralysis, VVIR PM | AD-EDMD | LMNA C1583G mut (exon 9) | Sanna et al,2003 |
| 2 | 24 | Male | Mild muscular involvement | Atrial paralysis, VVIR PM | XL-EDMD | STA 29 bp deletion | Boriani et al,2003 |
| 3 | 32 | Male | Severe skeletal dystrophy ( wasting humeral muscles, elbows contracture, thinning lower legs, and distal muscle weakness) | Atrial paralysis, VVIR PM | Atrial paralysis, VVIR PM | Unknown | Marshall et al, 1992 |
| 4 | 26 | Female | Severe skeletal dystrophy | Atrial paralysis, VVIR PM | Familial (possibly autosomal dominant) | Unkown | Wozakowska-Kaplon et al,2011 |
| 5 | 26 | Female | Severe skeletal dystrophy (contracture of elbows, knees, heels with muscle wasting) | Atrial paralysis, VVIR PM | AD-EDMD | LMNA G122T (exon 1) | Present case |

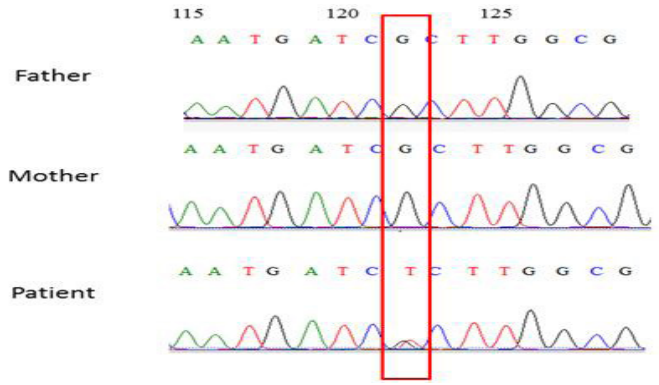


**Figure 3:** Electropherogram of molecular analysis in the trios sample. The patient's electropherogram shows the heterozygous missense c.122G>T,(p.Arg41Leu) mutation. Father and mother shows wild type (red box).

delineate the genotypes responsible for the atrial paralysis phenotype. In five EDMD patients with atrial paralysis (unfortunately two patients were genotypically unknown), the genomic positions were diverse. Two patients (patients 1 and 5) carried a mutation in the LMNA gene but in the different genomic position. Patient 1 carried a mutation in the carboxy-terminal tail domain of lamin A protein and Patient 5 (our case) carried a mutation in the central rod domain. Both patients had severe muscular dystrophy. We conclude that there is no clear correlation in hypothetical domain-specific phenotype related to EDMD manifestations.

Atrial paralysis and other forms of bradyarrhythmias carry significant risk of systemic embolism in EDMD with cardiac

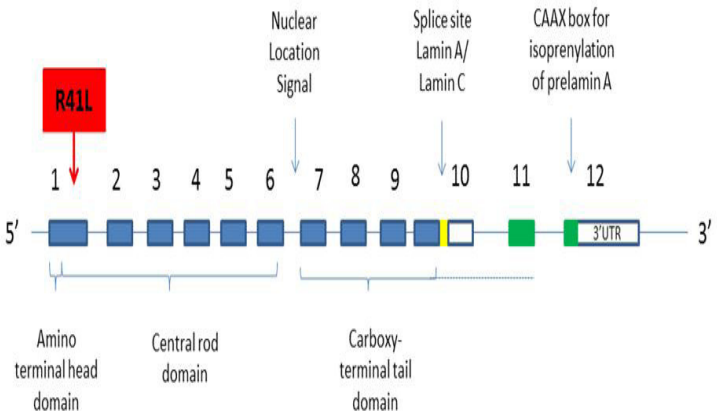


**Figure 4:** Illustration shows mutation in our patient (red box) is located in the central rod domain on the schematic of the genomic organization of the LMNA gene. The nuclear location signal, the splice site for the different generation of lamin A and lamin C, and the CAAX box for the isoprenylation of prelamin A are indicated by arrows. Blue areas indicate the sequences identical for both lamin A and lamin C. Regions coding for lamin C specific amino acids are indicated by yellow box. Regions coding for prelamin A specific amino acids are indicated by green box.

involvement.[13] Therefore, anticoagulation therapy is highly recommended.

In summary, we report a novel mutation in LMNA gene following autosomal dominant form of EDMD with atrial paralysis as a rare feature. Prevention from systemic embolism is important in EDMD patients with atrial paralysis. Functional analysis study for the future is needed to determine genotype-phenotype correlation. Early diagnosis, intervention, targeted management, and counseling are necessary for a better health and life quality of individuals with EDMD.

## Conflict Of Interests

None.

## Disclosures

None.

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