

Arrhythmogenic Left Ventricle Induced By Desmoplakin Mutation

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Desmoplakin (DSP) is an essential component of the cardiac desmosome and contributes to mechanical coupling between cardiomyocytes.

Pathogenic variants in DSP are associated with a distinctive form of arrhythmogenic cardiomyopathy characterized by predominant left ventricular involvement, myocardial fibrosis, ventricular arrhythmia and progressive ventricular dysfunction [1-3].

The patient will presented by a variant of presentation.

But, the most important thing is the early detection as the permanent damage of the cardiomyocyte is irreversible and need further treatment. The end result of untreated cases will be long life anti-failure and anti arrhythmic medication.

Keywords: Heart Failure, Cardiomyopathy and Desmoplakin.**Introduction**

DSP cardiomyopathy may initially present with episodes of chest pain and elevated cardiac troponin that resemble acute myocarditis. This inflammatory or “hot-phase” phenotype is an important diagnostic clue, particularly in children and adolescents with recurrent myocardial injury [1,4,5].

Cardiac magnetic resonance (CMR) imaging frequently demonstrates a non-ischemic pattern of myocardial fibrosis, commonly involving the subepicardial or mid-myocardial layers of the left ventricle. The presence of late gadolinium enhancement may precede severe ventricular dysfunction and can therefore contribute to early recognition [1,2].

Treatment of DSP- related heart failure is primarily guided by the patient’s ventricular function, symptoms, congestion, and arrhythmic risk.

Guideline-directed pediatric heart-failure therapy may include renin-angiotensin system inhibition or sacubitril/valsartan, beta-blockers, mineralocorticoid receptor antagonists and diuretics when clinically indicated [9].

Patients with significant ventricular arrhythmias require careful electrophysiological assessment and longitudinal rhythm monitoring. Interatrial device (ICD) implantation may be considered in selected high-risk patients after individualized assessment of ventricular function, ventricular arrhythmia burden, myocardial fibrosis, genotype and family history [2,9].

Discussion

Pediatric DSP cardiomyopathy may be particularly difficult to recognize because the initial phenotype can resemble acute myocarditis. Recurrent troponin elevation, ventricular arrhythmias, unexplained LV dysfunction and a family history of cardiomyopathy should increase suspicion for an inherited cardiomyopathy [4,5,7].

Pathogenic DSP variants disrupt desmosomal integrity and impair the mechanical connection between cardiomyocytes. This may lead to cardiomyocyte injury, inflammatory activation, progressive myocardial fibrosis, electrical instability and ultimately ventricular dysfunction and heart failure [1,3,6].

Genetic testing is therefore important in selected children with cardiomyopathy because identification of a pathogenic variant can establish the molecular diagnosis and facilitate cascade

screening of family members [7,8].

The DSP mutation include four types that different from one to another :

The first one is DSP c.2497C>T (p.Gln833Ter) is nonsense mutation

The second one is DSP c.2848del (p.Ile950LeufsTer27) is a frame-shift mutation

The third one is DSP c.5212C>T (p.Arg1738Ter) is a nonsense mutation

The fourth one is DSP c.939+1G>A is a splice-site variant mutation

Each mutation has a characteristic features as the following:

1- DSP c.2497C>T (p.Gln833Ter)

- Gene: DSP — *desmoplakin*
- Transcript: NM_004415.4
- Variant: c.2497C>T
- Protein: p.Gln833Ter, also written p.Gln833*
- Type: Nonsense
- Effect: Introduces a premature stop codon → predicted truncated/absent desmoplakin.
- ClinVar: classified Pathogenic.
- Genomic location: chromosome 6p24.3.
- dbSNP: rs1561693779.

This result in premature termination at amino acid 833 and loss of functional DSP protein impaired desmosomal integrity result in cardiomyocyte injury and fibrosis. The end result is arrhythmogenic cardiomyopathy.

2- DSP c.2848del (p.Ile950LeufsTer27)

- Transcript: NM_004415.4
- Variant: c.2848del
- Protein: p.Ile950LeufsTer27
- Type: Frame shift
- Effect: Deletion shifts the reading frame and introduces a premature termination codon 27 amino acids later and loss of desmosomal function.
- Reported in individuals with arrhythmogenic right ventricle cardiomyopathy.
- dbSNP: rs397516927.

3- DSP c.5212C>T (p.Arg1738Ter)

- Transcript: NM_004415.4
- Variant: c.5212C>T
- Protein: p.Arg1738Ter
- Type: Nonsense
- Effect: Premature stop codon at amino acid 1738.
- Genomic location: chromosome 6p24.3.

4- DSP c.939+1G>A

This one is particularly interesting because it is a splice-site mutation.

- Transcript: NM_004415.4
- Variant: c.939+1G>A

- Type: canonical donor splice-site variant
- Location: intron 7
- dbSNP: rs727504443.

DSP-related cardiomyopathy should be considered in children with unexplained LV dysfunction, ventricular arrhythmias, recurrent myocarditis-like episodes, or characteristic non-ischemic myocardial fibrosis on CMR and show subepicardial/mid-myocardial late gadolinium enhancement, often infero-lateral [1,2,4].

Early recognition through CMR and genetic testing may facilitate appropriate heart-failure treatment, prevention of arrhythmia family screening is highly recommended [7–9].

Conclusion

The prognosis of the patient condition will be good as there is early suspicion and management.

The symptoms are similar between myocarditis and DSP-related cardiomyopathy. The challenge in diagnosis is in CMR. Therefore, not hesitate to do a confirming CMR and start medication to persevere the cardiac cell.

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