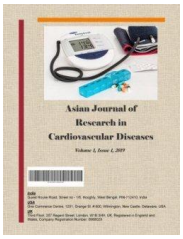

Asian Journal of Research in Cardiovascular Diseases

3(2): 27-31, 2021; Article no.AJRCD.72134

Homozygous PKP2 Deletion Associated with Left Ventricular Noncompaction and Arrhythmia

Abdalrahman Ali Ahmed Alhassan[1*], Tajudeen Bushari[1], Sami M. Al-Ahmari[1] and Motea E. Elhoury[1]

[1]Pediatric Cardiology Department, Prince Khaled Bin Sultan Cardiac Centre, Armed Forces Hospital - Southern Region, Khamis Mushayt, P.O.Box 101, Zip Code: 61961, Saudi Arabia.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Dr. Irina-Iuliana Costache, "Gr. T. Popa" University of Medicine and Pharmacy, Romania.
Reviewers:
(1) Carlos Darcy Alves Bersot, Hospital Federal da Lagoa, Brazil.
(2) Polliana Mihaela Leru, Carol Davila University of Medicine and Pharmacy, Romania.
Complete Peer review History: https://www.sdiarticle4.com/review-history/72134

Case Study

Received 23 June 2021
Accepted 30 August 2021
Published 03 September 2021

ABSTRACT

Left ventricular noncompaction cardiomyopathy (LVNC) is a genetic cardiomyopathy, characterized by prominent left ventricular trabeculations and deep intertrabecular recesses. Relatively few responsible genes have been identified. Plakophilin-2 (PKP2) is a component of the desmosome complex and is known for its role in cell-to-cell adhesion. Heterozygous variants of the PKP2 gene deletion that encoding the desmosomal protein plakophilin-2, are associated with arrhythmogenic right ventricular cardiomyopathy (ARVC). The homozygous variant of the PKP2 deletion has been described only once in a case associated with LVNC.

Here, we are reporting a total homozygous PKP2 deletion, after molecular genetic analysis of whole-exome sequencing (WES), which was identified in a 4- month boy with severe (LVNC). He presented with intractable congestive heart failure (CHF) and arrhythmia of Wolf – Parkinson - White syndrome (WPW) and ventricular tachycardia (VT). Our results support not only the association of PKP2 with ventricular noncompaction cardiomyopathy, but also WPW and VT.

Keywords: Left ventricular noncompaction; arrhythmogenic right ventricular cardiomyopathy; WES; PKP2 deletion.

**Corresponding author: E-mail: abdelrahmanalhassan10@gmail.com;*

1. INTRODUCTION

LVNC is a rare congenital cardiomyopathy. It is assumed to be result from failure of the myocardial compaction process between the 5th and 8th week of gestational age [1]. It has been defined as a genetic cardiomyopathy by the American Heart Association since 2006 2 Multiple genetic mutations have been implicated in the LVNC phenotype. It can be due to autosomal-dominant, autosomal-recessive, X-linked, or mitochondrial inheritance [2,3]. However, relatively few responsible gene mutations have been identified. On the other hand, the PKP2 gene mutation is known to be associated with arrhythmogenic right ventricular cardiomyopathy (ARVC) in heterozygous variants. The homozygous variant of PKP2 deletion is very rare and has been described only once in association with LVNC [4].

2. CASE PRESENTATION

We are reporting a case of a 4 months-old, full-term male infant of second-degree related parents (Fig. 1). He was born via normal spontaneous delivery. The mother had one baby who died early and one abortion. The fetal ultrasound of the baby was reported as normal and discharged after delivery with no concerns. The baby was admitted at age of 9 days with a history of hypoactivity, shortness of breath, and poor feeding. He was diagnosed to have congestive heart failure secondary to LVNC. In addition large and multiple mid muscular ventricular septal defects (VSD), and severe pulmonary hypertension were detected on echocardiography (echo). His electrocardiogram (ECG) was initially normal. He required ICU admission for one month to control his refractory heart failure and was discharged with anti-failure medication and L-carnitine therapy.

The first baby of this family was a girl, who died at the age of 20 days with suspected acute myocarditis. She presented to ER in a shock state and died within few hours. Her chest X-ray (CXR) showed cardiomegaly. His is the only available information because the baby died immediately before completing the investigations. The second pregnancy was spontaneous abortion at 8 weeks of gestation, but neither autopsy nor genetic test were done for both of them. The parents confirmed that there was no family history of cardiac arrhythmia or sudden death (Fig. 1).

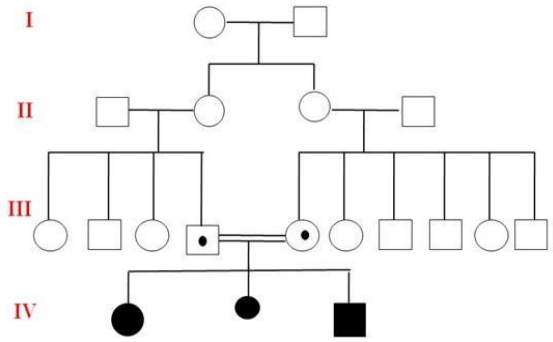

Fig. 1. Pedigree of the family. The affected sibs are marked with black symbols, the suspected affected abortion marked with small black symbols, the heterozygous carriers are marked with a central dot. the father sibs age range from 22 to 49 years, the mother sibs age range from 18 to 32 years, and the two grandmothers are 55 and 60 years old. Except for the parents, the other family members were not screened

The patient we are reporting was admitted to our cardiac center at the age of 4 months with symptoms of decompensated CHF (Ross HF class 111/1V) and generalized wasting. His weight was 4.2 kg (less than 5th centile). He had no dysmorphic features. The cardiovascular examination showed a heart rate of 180 beet/min, loud P2 and systolic murmur at the left sternal border, and enlarged liver. The ECG revealed features of WPW with short PR intervals and delta waves (Fig. 2). CXR showed cardiomegaly with biventricular hypertrophy. Non sustained VT with left branch block pattern was reported in the ECG Holter monitoring.

On echocardiography (Fig. 3), The left ventricle features fulfill Jennie's criteria of noncompaction cardiomyopathy (Bilayered myocardium with multiple prominent trabeculations in end-systole, non-compacted/compacted ratio of >2:1 and communication with the intertrabecular space demonstrated with color Doppler) [5]. The Left ventricular (LV) systolic function was moderately impaired with hypocontractility of the LV. The ejection fraction (EF) was 40% and there was severe pulmonary hypertension (estimated right ventricular systolic pressure of 90 mmHg). A large mid-muscular VSD with a bidirectional shunt was documented. His troponin-I level was 1614.3 pg/ml (normal range 14-42.9 pg/ml) and creatine kinase was 329.7 U/L (normal level 41-277 U/L). The metabolic screening was normal.

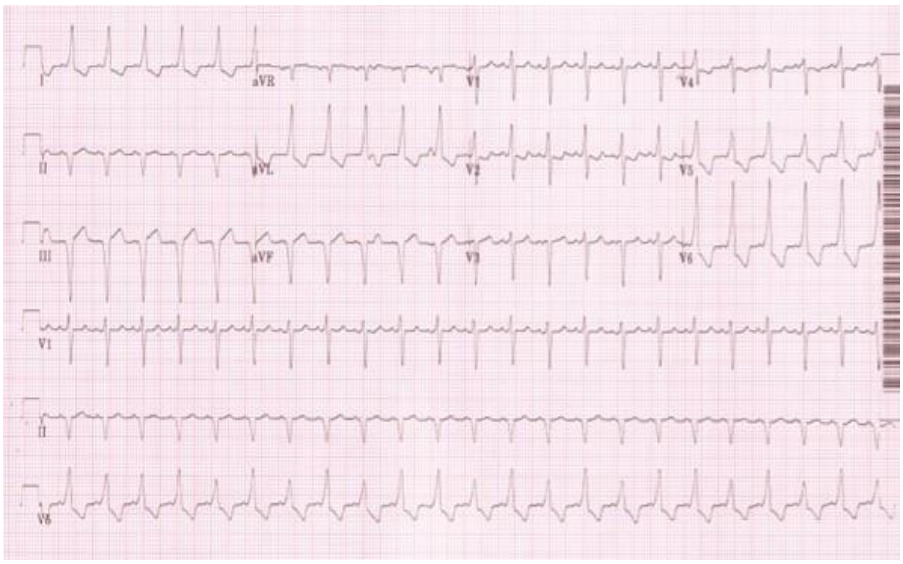

Fig. 2. ECG: showed features of WPW with short PR intervals and delta waves, heart rate of 180 beats/min, and left axis deviation

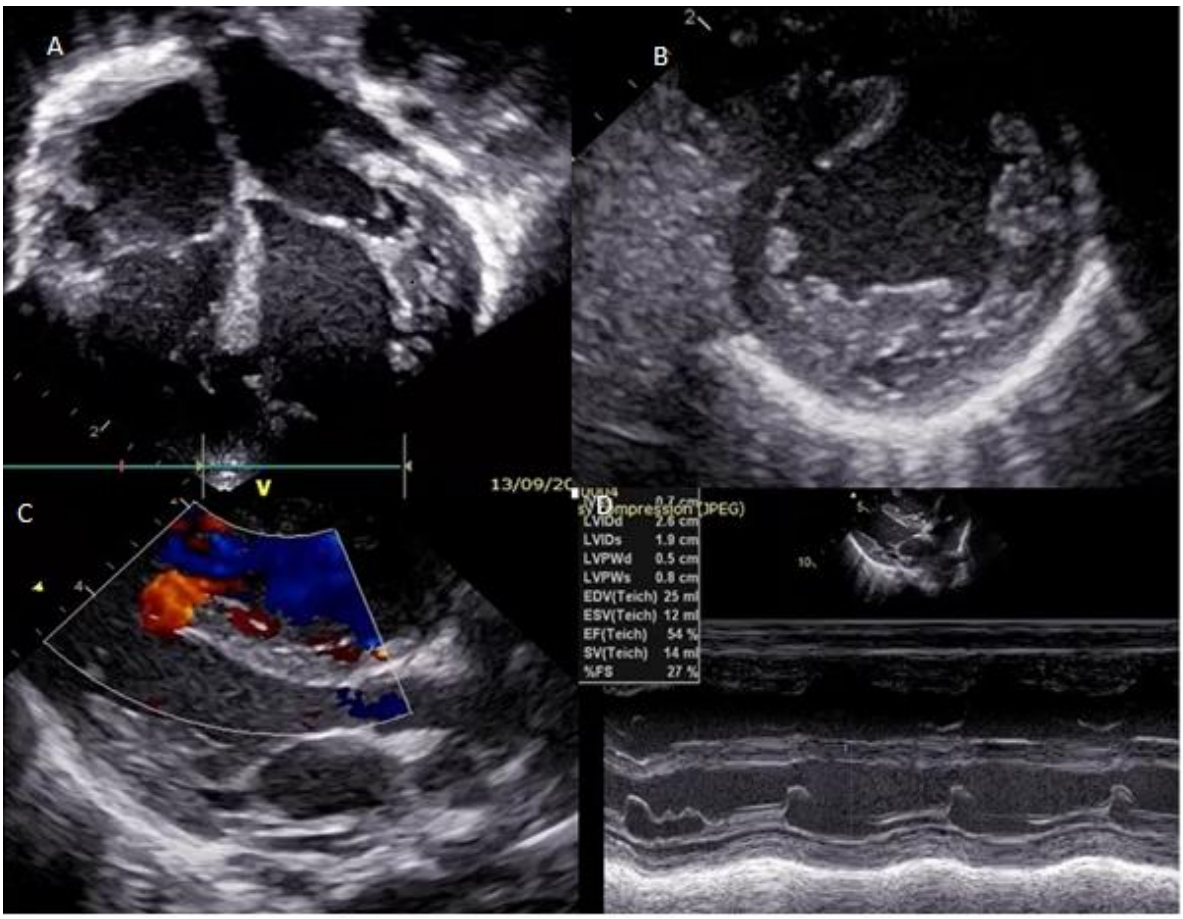

Fig. 3. Echocardiography: (A) four-chamber view; showed dilated left side, non-compacted LV myocardium, and mid muscular VSD. (B) Short-axis view; showed the non-compacted to a compacted ratio of 2:1 (C) long-axis view; showed mid muscular VSD with, a left to right shunt. (D) M mode; show improvement of EF of 54% after treatment

The patient was admitted to the pediatric ICU. He required aggressive management to control his CHF symptoms and pulmonary edema (Frusemide infusion, metolazone, captopril, and spironolactone). In addition to aspirin was added to prevent thrombus formation. Because of his arrhythmia, he was started on amiodarone infusion of 15 mic/kg/min and propranolol 1mg/kg/dose, as there was a paradoxical septal motion by Echo, which might be one attributable factor to his LV dysfunction secondary to electrical dyssynchrony [6]. Within few days after admission, The ECG showed marked improvement with the disappearance of short PR intervals and delta wave. The ejection fraction improved to 55%. Amiodarone infusion was tapered off and oral amiodarone was commenced with a 4 mg/kg dose.

The extensive molecular analysis was performed by WES of more than 20000 genes of the patient's DNA (biosceintia international, Ingelheim, Germany). It identified the homozygous variant c.1264-1268del p.(Leu422llefsTer2) in PKP2 (OMIM:602861) in chr12:33003809. That leads to a sequence of variant disruptions of the translation reading frame. Parallel analysis of parental WES data revealed that both parents are heterozygous for the detected variant in PKP2 (NM_004572.3). This confirms the homozygosity of the detected variant in our patient. The Allele frequency of this variant in the general population has not been documented in a homozygous state. This variant is classified as likely pathogenic, and according to ACMG guidelines [7]. No other pathogenic or likely pathogenic variant in the genes was detected.

Both parents (27 and 32 years) are asymptomatic heterozygous carriers (i.e. absence of arrhythmogenic right ventricular cardiomyopathy/ dysplasia (ARVC/D) or Brugada syndrome (BrS), according to the revised Task Force criteria. This may be due to incomplete penetrance. However, both parents may require long-term follow-up as the disease may manifest later.

3. DISCUSSION

Desmosomes are intercellular junctions of epithelia and cardiac muscle and they have specific role in strong adhesion and their failure can result in diseases of the skin and heart [4]. Structurally; they are composed by three major protein families: desmosomal cadherins, and Desmoplakins and armadillos proteins [8,9]. Plakophilin-2 (PKP2) is a component of the desmosome complex known for its role in cell-to-cell adhesion [10], The PKP2 gene has been firstly recognized in 1996) [11]. The main function of PKP2 is to provide the stabilizing force with the desmosomal-intermediate filament assembly facilitating cell-to-cell contact. An additional function is to regulate intracellular signaling and cellular electrophysiology [9,10]. Alterations in the PKP2 gene, in the heterozygous state, have been recognized for their pathological role in inherited cardiac conditions like ARVC/D (OMIM; 609040), BrS, idiopathic ventricular fibrillation, hypertrophic cardiomyopathy, and sudden death [4].

It has been proven that knock-out mice homozygous for pkp2 result in lethal defects in heart morphogenesis [12]. Judith M.A et described two siblings with hypoplastic left heart syndrome and features of noncompaction due to a homozygous truncating variant in PKP2 [12]. Ramond F. et al reported homozygous PKP2 deletion in two siblings with severe LVNC starting prenatally and leading to neonatal death due to rapid heart failure in a female baby and the other male fetus underwent termination of pregnancy after an intra-uterine diagnosis of LVNC [7], Our patient had a homozygous PKP2 mutation, c.1264-1268del p.(Leu422llefsTer2) modifying the splicing of exons and leading to a frame-shift mutation similar to but not identical to that previously published by Ramond F et al. [4], We consider this homozygous loss of PKP2 gene is responsible for the severe phenotype of LVNC in this case. Our findings support the previous report by Ramond F et al. that Homozygous PKP2 deletion is associated with abnormal myocardial development and left ventricle non-compaction [4], but also with WPW and VT. But we disagree with the previous report that advocates termination of pregnancy as the disease's prognosis remains uncertain.

4. CONCLUSION

This case describes an extremely rare association between homozygous PKP2 mutation, c.1264-1268del p.(Leu422llefsTer2), and left ventricle non-compaction. To the best of our knowledge, this is the second known case that illustrates this association, and it may link this gene mutation with WPW and VT.

CONSENT

As per international standards, the patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/72134