ARRHYTHMOGENIC RIGHT VENTRICULA DYSPLASIA/CARDOMYOPATHY: Clinical Presentation of Four Siblings with Different Clinical Presentation and Review of the Literature

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Summary

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC) is a cardiomyopathy characterized pathologically by fibrofatty replacement primarily of the RV and clinically by life-threatening ventricular arrhythmias in apparently healthy young people. The disease is typically inherited as an autosomal dominant trait with variable penetrance. We report four siblings with ARVC in one family with different clinical features: Sibling A had developed sudden cardiac death 19 years ago, at age 18. Sibling B, a 14-year-old girl admitted with multiple congestive heart failure attacks over a two-year period, finally developed fatal ventricular fibrillation at age 16. In sibling C, a 16-year-old girl with fatigue, palpitation and prominent ascites recently, typical features of ARVC were noted on ECG and nonsustained ventricular tachycardia on Holter recording. Echocardiography revealed dilated cardiomyopathy with prominent right chamber dilatation and magnetic resonance showed fatty replacement of right and left ventricular myocardium. The patient, diagnosed as having ARVC with left ventricular involvement, is currently on sotalol and congestive heart failure medication. Sibling D, a 9-year-old girl, screened because of her elder sister, was asymptomatic but her ECG, TTE and MRI revealed early phase of ARVC. In summary, the natural history of ARVC can be asymptomatic, subclinical-resulting in sudden death, overt with life-threatening arrhythmias, or dominated by progressive congestive heart failure. ***(Arch Turk Soc Cardiol 2003;31: 409-14)***

Key Words: *ECG, arrhythmogenic right ventricular dysplasia, cardiomyopathy, MRI*

Özet

Aritmojenik Sağ Ventriküler Displazisi / Kardiyomyopatisi: Farklı Klinik Görünümlü Dört Kardeşin Klinik Özellikleri ve Literatür Derlemesi

Aritmojenik sağ ventrikül displazisi/kardiyomyopatisi (ARVC) , primer olarak sağ ventrikülün "fibrofatty" -fibrosis ve yağlanma- yönünde patolojik değişimi ve sağlıklı görünümde olan genç populasyonda yaşamı tehdit eden ventriküler aritmi ile karakterize bir kardiyomyopatidir. Hastalık tipik olarak değişik penetranslı, otozomal dominant geçiş gösterir. Hastalığı oldukça değişik klinik özelliklerle yansıtan aritmojenik sağ ventrikül displazisi/kardiyomyopatili 4 kardeşi içeren bir aileyi bildiriyoruz: Kardeş A (bayan) 18 yaşındayken, 19 yıl önce, ani kardiyak ölüm öyküsü mevcut. 10 yıl sonra 14 yaşındaki Kardeş B (bayan) kalp yetmezliği tablosuyla başvurdu. Takibi boyunca tekrarlayan kalp yetmezliği atakları gözlendi. 2 yıl sonra ventriküler taşikardi atağı, ölümle sonlanan ventriküler fibrilasyona

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dejenere oldu. Kardeş C (16 yaş, bayan), 5 ay önce halsizlik, çarpıntı ve belirgin assit gelişti. EKG, tipik ARVC özellikleri gösteriyordu. Ekokardiyografide (TTE) sağ boşluklarda daha belirgin genişlemeyle beraber dilate kardiyomyopati saptandı. Holterde süreksiz ventriküler taşikardi epizodlarıyla beraber sık ventriküler ekstrasistoller izlendi. Magnetik rezonans görüntülemede (MRI) her iki ventrikülde adipoz değişim gözlendi. Sol ventrikül tutulumu gösteren ARVC tanısı konuldu. Halen kalp yetmezliği tedavisi ve sotalol altında olup genel durumu iyidir. Asemptomatik olan Kardeş D (9 yaş, bayan) ARVC'li ablası nedeniyle tarandı. EKG, TTE ve MRI, ARVC'nin erken faz bulgularını gösteriyordu. Sonuç olarak ARVC'nin doğal öyküsü; asemptomatik, subklinik seyredip ani ölümle sonlanma, açıkça hayatı tehdit eden ventriküler aritmi veya konjestif kalp yetersizliği ağırlıklı seyir gösterebilir. ***(Türk Kardiyol Dern Arş 2003;31: 409-14)***

Anahtar kelimeler: *Aritmojenik sağ ventrikül displazisi, EKG, kardiomyopati, MR*

REPORT of CASES

Arrhythmogenic right ventricular (RV) dysplasia/cardiomyopathy (ARVC) is a myocardial disease affecting primarily the RV and characterized by the gradual replacement of myocytes by adipose and fibrouse tissue that lead to structural and functional abnormalities of the RV[1]. The ARVC has been found to be genetic in 30% to 50% of individuals and is transmitted from one affected parent to a child as a dominant with incomplete inheritance[2]. The characteristic clinical findings include a variety of RV arrhythmias, global or regional RV and left ventricular (LV) involvement that may culminate in biventricular heart failure and electrocardiographic (ECG) evidence of depolarization or repolarization abnormalities[1].

We report four siblings those having different features of ARVC in one family. The parents and grandparents have no history of heart disease. Furthermore, physical examination, ECG and echocardiograms (TTE) of the parents were all negative for cardiac dysfunction. We screened the status of their 42 secondary relatives by ECG and TTE. All of them were free of cardiac diseases. There are eight siblings in all. Afflicted individuals were 3 young sisters and one boy. Afflicted siblingswere coded as A, B, C, D.

Sibling A was a 18-years-old girl who had developed sudden palpitations and syncope during walking 19 years ago. She had no previous cardiac history. During transferring to hospitals within one hour cardiopulmonary arrest had occured. Despite all medical efforts, the patient resulted in exitus. The patient had been accepted as sudden cardiac death without obviouse cardiac diagnosis. Ten years later, sibling B, a 14-year-old girl who developed progressive fatigue and dyspnea was admitted to emergency room. Her physical examination findings were consistent with biventricular heart failure. Her ECG revealed Q pattern in leads 2, 3, and aVF; incomplete RBBB and negative T waves in V1, V2, and V3. On TTE, dilatation of all four chambers dilatation with prominent right chamber involvement was observed. Left ventricular ejection fraction was 25%. Her condition was diagnosed as dilated cardiomyopathy and treated with ACE inhibitor. Two years later, the patient developed congestive heart failure and was evaluated at our instutition. There were severe dilatation of both ventricles, left ventricular ejection fraction of 15%, severe mitral and tricuspid regurgitation and restrictive type diastolic dysfunction. She was treated with anti congestive heart failure medication. Two weeks later after discharge she had admitted to the emergency department with the same but more severe symptoms. In the hospitalized period, cardiac monitoring showed sustained monomorphic ventricular tachycardia that degenerated into ventricular fibrillation, and she underwent D/C cardioversion with no success. Despite all efforts the patient had died. Her parents have not give consent for necropsy for sibling A and B.

Sibling C was a 16-year-old girl who developed fatigue, palpitation and prominent ascites five months ago. In her physical examination, there was prominent ascites

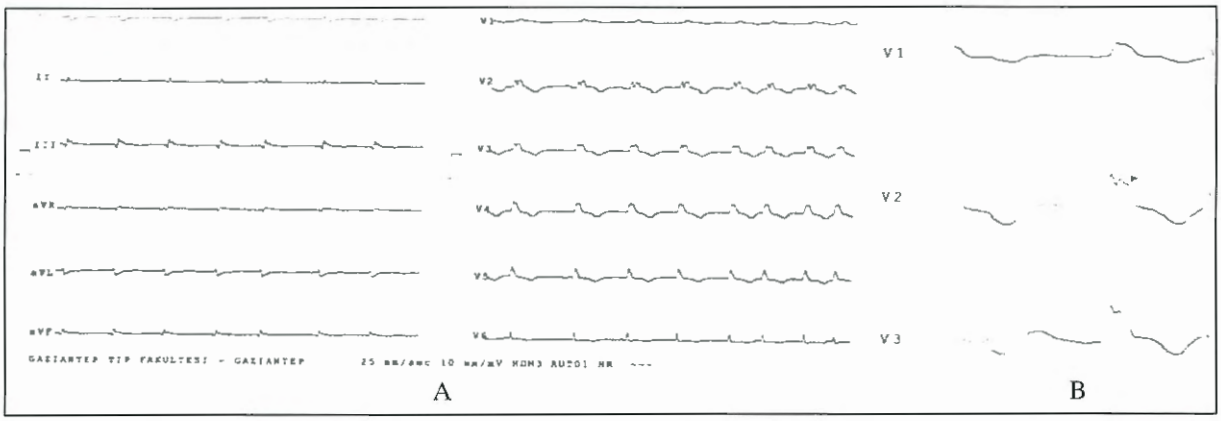

Figure 1: *ECG findings of Sibling C. A: low voltage QRS pattern with atrial fibrillalition, complete RBBB pattern and T-wave inversion in leads V1 to V6 and selective prolongation of the QRS in leads V1 to V3 compared with lead V6 are shown. B: ECG recorded with a spedd of 50mm/sec showed Epsilon wave in leads V2 and V3 (arrow)*

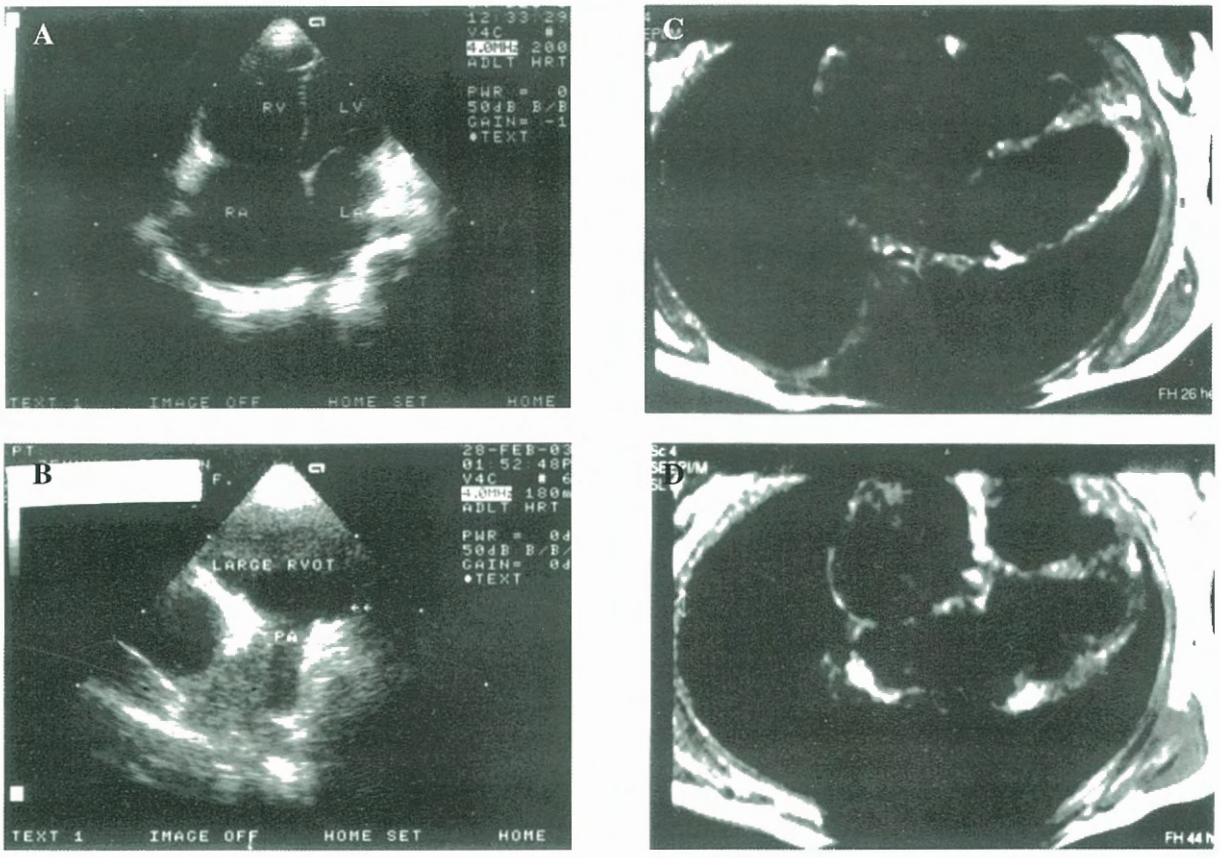

Figure 2: *Echocardiography and MRI findings of Sibling C. A: Apical four chamber view showed severely hypokinetic and dilated right ventricle. B: Aneurysm of the right ventricular outflow tract are shown. C, D: MRI showed fatty replacement of right and left ventricular myocardium and there was diffuse dalatation of the right heart chambers.*

and peripheral edema with an irregular rythm. There was no audibl murmur and lungs were clear to ascultation. ECG showed a very low voltage QRS pattern with atrial fibrillation. Complete RBBB pattern and T-wave inversion in leads V1 to V6 were observed (Figure 1A). On the ECG record with a speed of 50 mm/sec, Epsilon

wave in leads V2 and V3 were prominent (Figure 1B) and selective prolongation of the QRS duration in leads V1 to V3 compared to lead V6 were observed. Echocardiography showed severely hypokinetic and dilated right ventricle (Figure 2A) with aneurysm of the right ventricular outflow tract (Figure 2B). 24 hour ECG monitorisation revealed very frequent ventricular extrasystoles with some episodes of nonsustained ventricular tachycardia with left bundle branch block morphology, suggesting RV origin. Magnetic resonance Imaging (MRI) showed fatty replacement of right and left ventricular myocardium. In addition, there was diffuse dilatation of the right heart chambers (Figure 2 C, D). The patient was diagnosed as having ARVC with left ventricular involvement. The patient was initially treated with diuretics, ACE inhibitors, digoxine and spironolactone. For frequent ventricular extrasystoles, sotalol 80 mg bid p.o was iniated. During follow-up, her symptoms were improved significantly. After two weeks, efficacy of sotalol was determined by suppression of ventricular arrhythmias during repeated Holter monitoring and exercise testing. Sibling C is currently on sotalole medication and is doing well. Sibling D, a 9-years-old girl was screened because of her oldest sibling C having a diagnosis of ARVC. She was asymptomathic but her ECG revealed T wave inversions in leads V1 to V3 ECG recorded with speed of 50mm/sec showed premature Epsilon wave in leads V2 and V3. TTE revealed diffuse thinning of the RV myocardium with minimal dilatation of RVOT. MRI findings were consistent with TTE findings and showed minimal fatty replacement of RV. The patient was accepted as an early phase of ARVC. Although the patient was asypmtomatic and there was no demonstrable arrhythmia in repeated Holter recordings and exercise tests, beta blocker therapy was given and currently patient is doing well on beta blocker therapy.

DISCUSSION

In the present report, four siblings with ARVC with highly different clinical features were presented. Overall, all siblings, except sibling D which was considered to be in the early period of the diseases, showed severe manifestations of ARVC. These four cases comprise a unique familial grouping in what is already considered a very polymorphic disease[3]. Sibling A had presented with sudden death, probably secondary to ventricular arrhythmia, whereas sibling B had showed signs of biventricular heart failure and had masqueraded as dilated cardiomyopathy with a progressive and fatal outcome. Increasing attention is being devoted to the very typical ECG features of ARVC in siblings C and early ECG and TTE findings in asymptomatic period in sibling D.

The prevalance of ARVC in the general population is approximately 1 in 5000[4], but the disease is not widely recognized because of the difficulty in making the diagnosis[5]. Families with two or more affected individuals have been recognized in Asian, Japanese, Northern European, African and North American populations[4]. The gene responsible for ARVD have not been identified, but seven loci have been mapped to chromosome 14, 2, 3, and 10.[6]. Genetic products of these sites have not been easily identified because of incomplete penetrance and expression, age related expression and difficulties with accurate diagnosis of the disease. ARVC can progress to diffuse RV and LV involvement and may culminate in biventricular heart failure[7]. In this advanced stage, ARVC is diffucult to distinguish clinically from dilated cardiomyopathy[8]. ARVC typically occurs in young adults. At least %80 of cases are diagnosed before age 40. ARVC should be considered in young patients presenting with syncope, VT, cardiac arrest or in adult with CHF [9]. The VT in patients with ARVC usually has a LBBB morphology. The mechanism of sudden death in ARVC is, in most of cases, acceleration of VT with degeneration into VF[9]. Functional and structural worsening of RV performance is the major risk factor for cardiac arrest in patients with ARVC[10]. Arrhythmia is due to sympathetic stimulation in most patients[11]. Progressive loss of contractile function because of myocardial fibrofatty infiltration leads to dilatation and failure of the affected chambers. Right heart failure

typically presents in ARVC four to eight years after the appearence of RBBB on the ECG[10]. Clinician should consider the possibility of ARVC if the patient has an apparent dilated cardiyomyopathy with resting ECG showing right precordial T-wave abnormalities. Repolarisation abnormalities manifested by T-wave inversion in leads V1 to V3 in the absence of a complete RBBB are a minor diagnostic criteria but are useful in raising the suspicion of ARVC and are present up to 54% of cases[4]. Along with repolarisation abnormalities and conduction delays, there may also be low voltage in QRS related to the loss of RV myocardium. Selective prolongation of the QRS duration in leads V1 to V3 compared with lead V6 is an additional major criterion[12]. Epsilon wave are a major diagnostic criterion that are found in up to 30% of cases of ARVC[4]. Epsilon wave are postexcitation electrical potentials of small amplitude that occur at the end of the QRS complex and at the beginning of the ST segment. They are highly specific for ARVC and reflect delayed RV activation. The most prevalent finding in TTE is a severely hypokinetic and dilated RV, although the spectrum of abnormalities may range from a normal to severe RV dilation and hypokinesis[13] The most suggestive TTE findings for ARVC include dilation of RV, with localised aneurysm and dyskinesis[4]. An MRI study can reveal abnormal contraction patterns and enlargement of the right side of the heart, as well as fatty infiltration of the muscle[14]. Patients diagnosed with ARVC are advised to avoid vigorous athletic activity because of the risk of sudden cardiac death. In the presence of arrhythmia or symptoms, treatment should be iniated with beta blockers or sotalol. Sotalol is one of the most effective drug[15]. Some individuals with ARVC will require an implanted cardioverter-defibrillator (ICD). At the present time, the precise identification of individuals with ARNC who need this device has not been determined. Electrophysiologists, should be involved in the medical care of the patient with ARVC. Efficacy of treatment should be determined by supression of arrhtyhmia during Holter monitoring or exercise testing. When ARVC has progressed to extensive involvement affecting both the right and left ventricles, heart transplantation is an option.

Clinical course of ARVC can be subclinical in symptoms. Disease may be manifested by life-threatening arrhythmias, sudden death and sometimes by progressive congestive heart failure. Systematic evaluation of family members leads to early identification of ARVD. In the setting of positive family history, even minor ECG and TTE abnormalities are diagnostic.

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