

Different clinical presentations of Naxos disease and Carvajal syndrome: Case series from a single tertiary center and review of the literature

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ABSTRACT

Objective: Naxos disease is an autosomal recessive, inherited, cardiocutaneous disorder, characterized by arrhythmogenic right ventricular cardiomyopathy, woolly hair, and palmoplantar keratoderma. Carvajal syndrome is characterized by palmoplantar keratoderma, curly hair, dilated cardiomyopathy, especially on the left ventricle side, and early morbidity. The aim of this study was to evaluate the cutaneous and cardiac findings and genotype-phenotype relationship of six patients diagnosed with Naxos/Carvajal syndrome.

Methods: A retrospective review of six cases diagnosed with Naxos/Carvajal syndrome at our institution from 2002 to 2012 was performed. Demographic data; presenting complaints; cutaneous and cardiac findings; electrocardiography, echocardiography, and genetic analysis results; and treatment data were obtained from patient files.

Results: The patient group was composed of 4 males and 2 females, ranging from 1.5 to 13 years, with a mean age 6.4 years. Typical cutaneous and hair findings were present in all patients. Two cases presented with ventricular tachycardia attack, and 2 cases presented with severe heart failure. Two cases had only cutaneous findings without cardiac involvement at diagnosis. An implantable cardioverter-defibrillator was implanted in one case due to ongoing recurrent ventricular tachycardia attacks despite various antiarrhythmic treatments. Three of the 6 patients died during the follow-up.

Conclusion: For cases with woolly hair and palmoplantar keratoderma, the physician should provide a cardiac assessment, considering Naxos/Carvajal disease associated with cardiomyopathy. When an early diagnosis is made, the life expectancy may be increased by treatment of heart failure and arrhythmias; also, genetic counseling should be performed. (*Anatol J Cardiol* 2015; 15: 404-8)

Keywords: Naxos disease, Carvajal syndrome, cardiomyopathy, woolly hair, keratoderma

Introduction

Naxos disease is a rare autosomal recessive form of arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC) with a cutaneous phenotype, characterized by woolly hair and palmoplantar keratoderma (1). The disease was first reported by Protonotarios et al. (2) in patients living in the Greek island of Naxos. In the ensuing years, cases were also reported from Turkey, Israel, Saudi Arabia, India, and Argentina (3-9). The prevalence of the disease may be as high as 1/1000 in the Greek Islands. Plakoglobin and desmoplakin are intercellular adhesion proteins, and genetic studies have focused on the genes that encode these proteins (3, 6). Herein, we discussed this rare disease by presenting the clinical features of our 6 cases.

Methods

The medical records of 5 pediatric cases diagnosed with Naxos disease and 1 pediatric case with Carvajal syndrome at Erciyes University Medical Faculty and Kahramanmaraş Sütçü İmam University Medical Faculty were analyzed. Demographic data; presenting complaints; cutaneous and cardiac findings; electrocardiography, echocardiography, and genetic analysis results; and treatment data were collected.

Results

We identified 6 cases (4 males, 2 females), ages 1.5 to 13 years old (average 6.4 years) with Naxos disease (5) and Carvajal syndrome (1). Demographic data and features at presentation are summarized in Table 1.



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Figure 1. a-c. Woolly hair (a) and palmar (b) and plantar (c) keratoderma in Case 1

Table 1. Clinic details in six patients with Naxos disease

Cases	Gender	Age at diagnosis, years	Complaint	Echocardiography at diagnosis	Clinical events	Antiarrhythmic treatment	Mutation analysis	Outcome	Duration, years
Case 1	Male	13	Palpitation, syncope	Dilated RV, An aneurysm of RV, Thrombus in RV, EF: 53%	VT	Amiodarone, Metoprolol, Dronedarone, ICD	Plakoglobin (Pk2157Del2TG)	Recurrent episodes of VT	11
Case 2	Male	6	Chest pain	Bright spot of RV wall, EF: 72%	none	-	Plakoglobin (Pk2157Del2TG)	Asymptomatic	11
Case 3	Male	6	Fatigue, weakness, edema of feet	Biventricular dilatation, thrombus in LV, EF: 27%	HF	none	Desmoplakin	Sudden death	2
Case 4	Female	1.5	none	Normal ECHO findings	none	none	Plakoglobin	Asymptomatic	2
Case 5	Male	3	Fatigue, weakness	Biventricular dilatation, EF: 37%	HF (FC IV), VT	Amiodarone	Plakoglobin (Pk2157Del2TG)	Sudden death	0
Case 6	Female	9	Palpitation, fatigue, weakness, syncope	Biventricular dilatation	HF (FC IV), VT	Amiodarone	Analysis could not be made	Sudden death	1

EF - ejection fraction; FC-(NYHA) - functional class; HF - heart failure; ICD - implantable defibrillator; LV - left ventricle; RV - right ventricle; VT - ventricular tachycardia

Two cases presented with ventricular tachycardia attack, and 2 cases presented with severe heart failure clinic. The other 2 cases had only cutaneous manifestations without cardiac involvement at diagnosis. All patients had typical cutaneous and hair findings. An implantable cardioverter-defibrillator was implanted in a patient due to ongoing recurrent ventricular tachycardia, despite various antiarrhythmic treatments. Three of the 6 cases died at the follow-up.

Case 1

A 13-year-old boy with no previous history of cardiac disease was admitted to our clinic with complaints of chest pain, palpitations, and syncope. He was the first child of parents with second-degree consanguinity and had a brother with similar cutaneous manifestations. On physical examination, the pulse rate was 208/minute, and hepatomegaly was detected. On auscultation, basal crepitant rales were present, and gallop rhythm was also present. Woolly hair and palmoplantar keratoderma

were noticed on inspection (Fig. 1). Electrocardiography (ECG) demonstrated ventricular tachycardia. Normal sinus rhythm was obtained by lidocaine administration. Echocardiography revealed right atrium and right ventricle dilatation with a saccular aneurysmal segment in the apex of the right ventricle, a thrombus 3 cm in diameter, normal left ventricle wall and cavity, and mildly decreased ejection fraction (EF) (53%). Under intravenous heparin treatment, the thrombus disappeared, and clinical signs improved in the following days. Genetic tests revealed heterozygous 2-base-pair mutations in the plakoglobin gene (Pk2157Del2TG) in the parents. The case and his brother were homozygous for the same gene mutations.

Five years after the diagnosis of Naxos disease, an implantable cardioverter-defibrillator was needed due to ongoing recurrent ventricular tachycardia attacks, despite various antiarrhythmic treatments. Currently, the ECG of the 23-year-old patient displays a rightward axis, prominent voltage suppression, and flattening of the T waves (Fig. 2). Echocardiographic

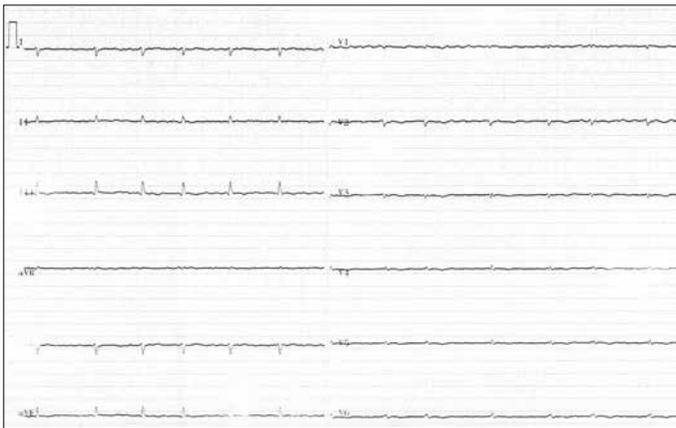


Figure 2. Electrocardiography of Case 1 shows rightward axis, prominent voltage suppression, and flattening of the T waves

examination reveals a border EF (54%), significant right atrial and ventricular enlargement, and global hypokinesia of the right ventricle muscle. This case and his brother (case 2) were published previously (4), but these 2 cases are presented here to share their clinical progression.

Case 2

A 6-year-old boy was evaluated when his brother was diagnosed with Naxos disease. Mutation analysis was performed for the presence of cutaneous findings of the disease, including woolly hair and palmoplantar keratoderma, and it confirmed the diagnosis of Naxos disease. It was learned that both he and his brother had woolly hair at birth, and keratoderma began at 6 months of age. Initial ECG and echocardiographic examinations were found to be normal. However, during 5 years of follow-up, the frequency of ventricular extrasystole increased, and non-sustained ventricular tachycardia attacks were detected by Holter records. The case had chest pain from time to time and non-sustained ventricular tachycardia on Holter, but the brother, with a severely affected heart, is currently taking beta-blockers for arrhythmia prophylaxis. In the last echocardiographic examination, a hypoechoic focus was noticed within the right ventricular muscle mass.

Case 3

A 6-year-old male was admitted with complaints of easy fatigue, weakness, and swelling. The physical examination revealed tachycardia, hepatosplenomegaly, and edema with a Godet sign associated with curly hair and keratoderma on the hands and feet. There was no consanguinity between the parents. He was a single child of the family. Echocardiography revealed biventricular dilatation, significantly decreased left ventricular function, second-degree mitral insufficiency, second-degree tricuspid insufficiency, and a thrombus 3 cm in diameter within the left ventricle. Anticongestive medications were administered and heparin was infused for the presence of thrombus. A follow-up echocardiographic examination revealed that the thrombus was resolved and that the heart failure was controlled with medications. The diagnosis of Carvajal syndrome was considered due to the physical findings and genetic

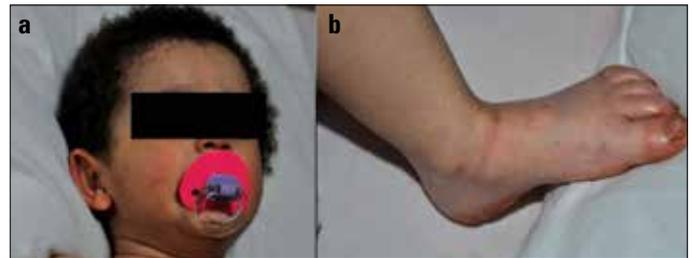


Figure 3. a, b. Woolly hair and plantar keratoderma in Case 4

studies, which demonstrated a desmoplakin gene mutation. Two years after the diagnosis, the patient presented with mumps-related deterioration and severe heart failure. The ECG of the patient revealed sinus tachycardia with northwest axis deviation, wide and pointed P waves, prolonged PR distance (0.20 sec), and flattening of T waves in V1-V3 and voltage suppression. The patient was unresponsive to treatment and died on the hospital admission day due to severe heart failure.

Case 4

An 18-month-old girl with diffuse hyperkeratotic yellowish lesions on the skin; fragile, thin, and dystrophic nails; and woolly hair was presented for further evaluation (Fig. 3). She had been followed and treated for psoriasis in another clinic, but no improvement was detected. In her physical examination, woolly hair and palmoplantar keratoderma was noted, but cardiac involvement was not detected yet. Electrocardiographic and echocardiographic examinations were within the normal ranges. Genetic testing revealed a plakoglobin gene mutation.

Case 5

A 3-year-old male case was referred to our clinic for uncontrolled heart failure and clinical deterioration. The patient was severely ill, weak, tachycardic, and tachypneic. In the assessment at admission, hepatomegaly, palmoplantar keratoderma, and woolly hair were detected. Teleradiography revealed severe cardiomegaly, and on the ECG, rightward axis deviation and ventricular tachycardia with right bundle branch block morphology were detected. Echocardiographic examination revealed dilatation of the ventricles, second-degree mitral and tricuspid valve insufficiency, and decreased left ventricle function (EF 37%). Ventricular tachycardia was controlled by amiodarone infusion, but the clinical outcome was poor. The patient suddenly died on the seventh day of hospitalization. Genetic testing revealed a heterozygous plakoglobin gene mutation (Pk2157Del2TG) in the parents and a homozygous gene mutation in the patient.

Case 6

A 9-year-old female case, whose parents were first-degree relatives, was assessed because of easy fatigue, weakness, palpitations, and syncope. Echocardiographic examination revealed severe dilatation of both ventricles and decreased left ventricle function. Despite the anticongestive therapy and antiarrhythmic treatments for the recurrent ventricular tachycardia attacks, the clinical deterioration could not be improved, and the patient died. Mutation analysis could not be performed.

Discussion

Arrhythmogenic right ventricular cardiomyopathy is a cardiac muscle disorder that is manifested as syncope and heart failure as the result of recurrent ventricular tachycardia and fibrillation, which may result in sudden death. It is characterized by a progressive replacement of myocardial cells with adipose and fibrous tissue (4, 9). Sporadic and familial forms of the disease have been reported up to the present. The familial form is usually inherited in an autosomal dominant manner (10).

In 1986, the autosomal recessive form was defined by Protonotarios et al. (2) in a family in the Greek island of Naxos. Naxos disease is characterized clinically by palmoplantar keratoderma, woolly hair, and ARVC. The same researchers mapped the genetic locus of Naxos disease to chromosome 17q21 and determined the plakoglobin gene mutation to be responsible for the disease (11). Mckoy et al. (12) showed that a homozygous 2-bp deletion (c.2157delTG) in the gene encoding plakoglobin underlies Naxos disease. Only one other plakoglobin mutation has been associated with human disease (13). Asimaki et al. (14) reported a novel autosomal dominant mutation (S39_K40insS) in the gene encoding plakoglobin in an ARVC-affected patient. In our cases, a plakoglobin gene mutation was detected in 3 of 4 in whom mutation analysis was performed (Pk2157Del2TG).

Norgett et al. (15) determined a different mutation responsible for left-dominant dilated cardiomyopathy, palmoplantar keratoderma, and woolly hair on chromosome 6p24, which is the desmoplakin gene. One of the desmoplakin gene mutations is a homozygous single-nucleotide deletion in the last exon of desmoplakin (c.7901delG), responsible for Carvajal syndrome. Other desmoplakin mutations associated with cardiocutaneous manifestation have been defined as a homozygous non-sense mutation (p.R1267X) and a compound heterozygous mutation (c.2516del4 and c.3917del4) in the literature (14). Few patients with this syndrome have been reported, mainly from Ecuador or India. Turkay et al. (16) reported a 7-year-old Turkish girl with Carvajal syndrome in 2006. A desmoplakin gene mutation was detected in one of our patients (Case 3).

Both plakoglobin and desmoplakin are involved in the desmosomal structure. Desmosomes are adhesive junction proteins crucial for the rigidity and resistance of skin and myocardial cells. A defect occurring in these proteins leads to the development of a pathological process in the heart, hair, and skin, particularly under increased mechanical stress and tension. While woolly hair is present at birth, keratoderma develops due to exposure to pressure during the first year of life, when infants start to use their hands and feet, in Naxos disease. The histological examination of the skin displays non-epidermolytic keratoderma. The characteristic phenotypic appearance was present in all of our cases.

Arrhythmogenic right ventricular cardiomyopathy, which is related to the homozygous plakoglobin gene mutation of Naxos disease, is a progressive heart disease with a poor prognosis. In one study, the rates of disease-related mortality and sudden death mortality per year were reported as 3% and 2%-3%,

respectively, in Naxos disease, and these were higher than in other ARVC series (3). The same study also reported that presentation with syncope, early structural progression under the age of 35, and left ventricular involvement are the best predictors of sudden death and poor outcome. In the population of Naxos, the ratio of heterozygous persons is about 5%. Although minor ECG and echocardiography alterations are observed in a small portion of individuals with a heterozygous plakoglobin gene mutation, they do not develop clinically significant disease (3).

Naxos disease initially begins from a localized region of the right ventricle and may progressively affect the entire right ventricle and then the left ventricle. Electrocardiography often shows an inverted T wave in V1-V3, wide QRS complex in V1-V3, epsilon wave, right bundle branch block and low voltage, and/or a flat T wave in left precordial derivations in severe ventricular involvement. Echocardiography findings may vary, ranging from mild dilatation of the right ventricle and regional hypokinesia to severe dilatation and diffuse hypokinesia. Left ventricle dilatation and hypokinesia have been additionally reported in some patients (17). Cardiac magnetic resonance may reveal ventricle enlargement with irregular trabeculation and increased intensity on T1-weighted images reflecting fibrofatty changes (18, 19). Histological examination of the heart in patients with Naxos disease exhibits a process involving the replacement of myocardial cells by adipose and fibrous tissue in the subepicardial and mural layers, beginning from the right ventricle (5).

The presentation of the disease may be seen as syncope, ventricular tachycardia, and clinical signs of heart failure or sometimes as sudden death. The cardiac manifestations may differ according to the responsible mutation. If the cause is a plakoglobin gene mutation, patients present with syncope and palpitation (caused by ventricular tachycardia). The clinical findings of cardiomyopathy are observed in adolescence, and the penetrance of the disease in individuals with a plakoglobin gene mutation is shown to be 100% (1). As reported in previous studies (3, 7), our cases (1 and 5) with a plakoglobin gene mutation presented with severe heart failure caused by ventricular tachycardia. Case 4 was a young sibling who had only cutaneous manifestations. Although the clinical features are supporting Naxos disease, she does not have any apparent cardiac involvement yet.

If the cause is a desmoplakin gene mutation, the predominant findings are related with heart failure (3). Case 3 died because of severe heart failure, due to a desmoplakin gene mutation. Arrhythmia was not predominant in this patient.

However, Case 5, who had a plakoglobin gene mutation associated with advanced cardiomyopathy also affecting the left ventricle at 3 years of age, demonstrated that the gene location of the mutation and the penetrance are directly related to the clinical presentation. A younger sibling (Case 2) was detected incidentally because of his severely affected brother. Case 6 was a poorly followed-up patient who was admitted in the terminal stage and had biventricular involvement with a typical phenotypic appearance. Protonotarios et al. (1, 3) think that the clinical heterogeneity of the disease is related with the different degrees of penetration of the disease in individuals.

The primary objective of treatment is the prevention of prolonged arrhythmia attacks and sudden cardiac deaths. An implantable cardioverter-defibrillator is indicated in patients with ventricular tachycardia. Cardioverter-defibrillator implantation was performed in our first patient. The need for emergency hospital admission due to ventricular tachycardia decreased, owing to the implantable cardioverter-defibrillator, which provided defibrillation during attack periods. Antiarrhythmic agents are used to prevent ventricular tachycardia attacks; diuretic agents and angiotensin-converting enzyme inhibitors are used to prevent heart failure; and acetylsalicylic acid prophylaxis is used to prevent intracardiac thrombus.

Thrombus may develop as a result of severe heart failure or recurrent and prolonged arrhythmias. Two of our cases had intracardiac thrombi that might have developed due to myocardial hypokinesia related to the advanced stage of cardiomyopathy. To prevent this complication, the heart failure must be strictly controlled, and also, antiarrhythmic medications must be considered in the follow-up, even when a cardioverter-defibrillator has been implanted. If the risk is high and the clinical presentation is severe, heart transplantation should be planned for these end-stage patients (4).

Study limitations

Our study has several limitations. First, the study population was small. Second, a genetic analysis could not be performed in all patients.

Conclusion

As a result, based on their heterozygosity, parents with a child with Naxos/Carvajal disease should receive genetic counseling before any future pregnancy. For cases with woolly hair and palmoplantar keratoderma, the physician should provide a cardiac assessment, considering Naxos/Carvajal disease associated with cardiomyopathy. When an early diagnosis is made, an increase in life expectancy may be provided by treatment of the heart failure and arrhythmias.

Ethical: The study protocol was approved by the Local Ethic Committee and written informed consent was obtained from all subjects.

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Conflict of interest: None declared.

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