A Rare Entity of Cardiocutaneous Syndromes; Carvajal Syndrome: Report of an Adult Turkish Patient

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ÖZET


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Kardiyokütanöz syndromlar, Carvajal Sendromu, senkop

ABSTRACT

Carvajal syndrome is a familial cardiocutaneous syndrome that consists of wooly hair, palmoplantar keratoderma and cardiomyopathy. This syndrome caused by a recessive deletion mutation in desmoplakin gene which is an intracellular protein that links desmosomal adhesion molecules to intermediate filaments of cytoskeleton. Altered protein-protein interactions at intercalated disks cause both contractile and electrical dysfunction of heart. In the presenting case report, we describe an adult case of Carvajal syndrome diagnosed in Turkey.

Keywords
Cardiocutaneous syndrome, Carvajal syndrome, syncope

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Introduction

Carvajal syndrome is a type of cardiocutaneous disorder consisting of wooly hair, palmoplantar hyperkeratosis and dilated cardiomyopathy mainly involving left ventricle (1-4).

Naxos disease has the same phenotypic findings but characteristically involving right ventricle and is included as recessive type arrhythmogenic right ventricular cardiomyopathy (ARVC) group (5-9). Because of high rates of sudden cardiac death in cardiocutaneous diseases, there are few case reports in the literature regarding adults. In this case report, we will present an adult Turkish patient with typical phenotype for cardiocutaneous disorders and diagnosed as Carvajal syndrome.

Case report

A 26-year-old married female patient admitted to our cardiology department with the complaints of palpitation, chest pain and fatigue for one year. She had also described syncopal attacks for 3 times in the last year. Her past medical history was free of any cardiovascular or systemic diseases except a diagnosis of dermatitis in her hands. She was not taking any medication and her family history did not reveal any disease. Physical examination was normal except hyperkeratosis in her palms and soles, diagnosed as dermatitis for several times, and thin, curly hair presenting since childhood (Figure 1-2). Laboratory examination for complete blood count, blood biochemistry and lipid profile were in normal limits. Chest X-ray revealed normal cardiac and pleuropulmonary fields. Electrocardiography disclosed sinus rhythm with QRS enlargement in right precordial leads and epsilon waves in leads V1 to V2 low voltage at precordial leads with negative T waves (Figure 3). Echocardiography showed dilated left ventricle with decreased left ventricular systolic functions (end diastolic dimension of 59 mm and ejection fraction of 40%) and wall motion abnormality (hypokinesia at mid-anterior septum and an-
terior wall). Holter examination disclosed frequent ventricular extrasystoles and one episode of nonsustained ventricular tachycardia (VT). Coronary vessels were normal in coronary angiography however left ventriculography showed a dilated ventricle with hypokinesia at anterior and anterolateral wall. According to those findings electrophysiologic study was performed to clear the etiology of syncopal attacks but found to be in normal limits without induction of VT or fibrillation. After all this work-up, a diagnosis of Carvajal syndrome was made according to the physical findings of palmar-plantar hyperkeratosis and wooly, curly, thin hair with dilated cardiomyopathy in this patient with a history of syncopal attacks and non-sustained VT in Holter recordings. Further investigation of family history disclosed sudden cardiac death of her cousin at an age of 27, having same phenotypic appearance. Cardiac magnetic resonance imaging of patient revealed wall motion abnormality of left ventricle with spared right ventricle. Because of syncopal attacks NSVT and a family history of sudden cardiac death, an implantable cardioverter defibrillator was implanted to the patient uneventfully and discharged on β-blocker therapy in good condition.

**Discussion**

Carvajal syndrome is first described by Dr. Luis Carvajal in families with recessive inheritance consisting of wooly hair, epidermolytic palmoplantar keratoderma and dilated cardiomyopathy (2). It is caused by a mutation in desmoplakin gene, a desmosomal protein which links desmosomal cadherins to cytoskeleton (10-12). Carvajal syndrome is similar to Naxos disease, a recessive type of ARVC, which has the same cutaneous findings (2,12). ARVC is a genetic disorder characterised by cardiomyopathy, ventricular arrhythmias and structural abnormalities of right ventricle (13). Diffuse or segmental progressive replacement of right myocardium with fibrosis and fatty tissue with myocardial cell loss is the hallmark of ARVC histopathologically. ARVC is an autosomal dominant disease causing sudden cardiac death, however it has autosomal recessive forms which are associated with desmoplakin and plakoglobin mutations. Naxos disease is recessive variant of ARVC with wooly hair and palmoplantar keratoderma and caused by a mutation in plakoglobin (7).
Carvajal syndrome is characterized by an autosomal recessive mutation of desmoplakin gene associated with intermediate filament binding site of cells with keratoderma on palms and soles, wooly hair and cardiac involvement of predominantly left ventricle, clinically overlapping with dilated cardiomyopathy (14). Patients may present with syncope, congestive heart failure or sudden death. In all patients palmoplantar keratoderma and wooly hair is seen with cardiomyopathy. Low voltage on precordial leads, intraventricular conduction defects and T wave inversions are commonly seen electrocardiographic abnormalities. Left ventricle is involved in the second decade of life in 90% of patients and 57 % percent of patients develop heart failure and most die during adolescence (14-15). When examined pathologically; ventricular hypertrophy, dilatation, focal ventricular aneurysms and ultrastructural abnormalities at intercalated disks are seen (16-17). In Carvajal syndrome, right ventricle shows similar abnormalities like ARVC as focal wall thinning and aneurnysmal dilatations. Microscopically, extensive myocardial loss, fibrosis in left ventricle and diffuse scaring of free walls of right and left ventricle is seen but fatty infiltration of right or left ventricular wall is not detected in contrast to ARVC. In immuno-histochemical analysis, desmoplakin is undetectable at intercellular junctions. Plakoglobin and connexin 43 -major gap junction protein is also markedly diminished with the preservation of N-cadherin, desmosomal cadherin and desmocollin. Although sarcomeric distribution of the intermediate filament protein, desmin, was normal in Carvajal syndrome, it was absent at intercalated disks (4).

Naxos disease and Carvajal syndrome both share a similiar pathophysiologic origin involving abnormalities in cytoskeletal elements having role also in signal transmission of cells. Adherens and desmosomes secure mechanical coupling of myocardium and gap junctions provide electrical coupling for contraction of cardiomyocytes as a syncytium. Plakoglobin is present in adherens and desmosomes desmoplakin is important for integrity of intermediate filaments. The abnormalities in the cell to cell junctions seem to disrupt tissue integrity and cause keratoderma in skin, replacement of fibrofatty tissue in myocardium and cause clinically apparent electrical disfunction as arrhythmias and contractile disfunction as heart failure (14).

There are several diseases caused by different types of mutations involving cytoskeletal elements having different modes of inheritance. Plakophilin -2 (PKP-2) mutation is related with nonsyndromic autosomal dominat ARVC and is found in half of the patients of dominant ARVC and familial forms of ARVC in Northern Europe. Desmoplakin and desmoglein-2 gene mutations are also seen in dominant ARVC. Deletion in plakoglobin gene causes a recessive type of ARVC with palmoplantar keratoderma and wooly; known as Naxos disease (18-22). Autosomal recessive mutation in intermediate filament binding site of desmoplakin gene causes Carvajal syndrome. Poll Hereford calves is a lethal type autosomal recessive cardiocutaneous syndrome affecting animals with distinctive wooly haircoat, ventricular dysrhythmias and neonatal keratitis; death occuring due to ventricular fibrilation or after a period of congestive heart failure (23).

In recent reviews, Carvajal syndrome and Naxos disease are described together as one entity with genetic and clinical heterogeneity with the findings of cutaneous disorders; palmoplantar keratoderma and wooly hair (24-25). In future ARVC, Naxos and Carvajal syndrome may
be classified under disease of cell adhesion molecule cardiomyopathies; because of the common mutations including cell adhesion molecules and cytoskeleton elements. In patients with cardiocutaneous syndromes, presence of syncope, left ventricular involvement and the appearance of symptoms and/or structural progression before the age of 35 years were risk factors for sudden cardiac death (14). Therefore ICD was implanted to our patient according to criteria involving syncope, family history of premature sudden cardiac death, left ventricular involvement and non sustained VT.

In conclusion this patient was diagnosed as Carvajal syndrome because of the predominance of left ventricular involvement together with cutaneous findings of wooly hair and palmoplantar keratoderma. There are few case reports regarding cardiocutaneous diseases including Carvajal syndrome in children from our country (26-27). To our knowledge, this is the first report of an adult patient diagnosed as Carvajal syndrome in Turkey.

REFERENCES


