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CASE REPORT

Cardiocutaneous Syndrome: Naxos Disease

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Abstract

Naxos disease is a recessively inherited condition, caused by mutation in genes encoding desmosomal proteins Plakoglobin. It is characterized by peculiar woolly hair, palmoplantar keratoderma with arrhythmogenic Right Ventricular dysplasia /cardiomyopathy. A syndrome (a variant of Naxos) with same cutaneous phenotype and predominant Left Ventricular involvement is CARVAJAL syndrome. Patients are at risk of sudden cardiac death due to cardiomyopathy. We herein report a rare case of Naxos disease in a 16 years old male born of a 3º consanguineous marriage, presented with features suggestive of congestive cardiac failure with clubbing (grade 1), woolly hair, and focal keratoderma over palms and soles. ECG demonstrated – inverted T waves (V1-V3), QRS prolongation and complete RBBB. Echocardiography revealed-severe biventricular dysfunction with EF-15-20%, severe MR, severe TR and PAH. Patient was treated with diuretics, ß blockers and ACE inhibitors. These children may need implantation of automatic cardioverter defibrillator to prevent arrhythmogenic attacks and sudden cardiac death. CONCLUSION: For child with woolly hair and palmoplantar keratoderma, the pediatrician should provide a cardiac assessment, considering Naxos/Carvajal disease associated cardiomyopathy. When an early diagnosis is made, life expectancy can be increased by treatment of Heart failure and arrhythmias.

Keywords: Naxos disease; Palmoplantar keratoderma; Cardiomyopathy; Wolly hair

Introduction

Naxos disease is a rare recessively inherited condition with arrythmogenic RV dysplasia /cardiomyopathy and a cutaneous phenotype, characterized by peculiar woolly hair and palmoplantar keratoderma. A syndrome with same cutaneous phenotype and predominant LV involvement is CARVAJAL syndrome. Mutation in genes encoding desmosomal proteins,

Plakoglobin and Desmoplakin, is the cause of the syndrome. Patients present with syncope, sustained ventricular tachycardia or sudden cardiac death. Patients are at risk of sudden cardiac death due to cardiomyopathy.

Case report

A 16-years-old male, born of a 3° consanguineous marriage, presented with abdominal distension and breathlessness of 5 months duration. At admission, child had Congestive cardiac failure with HR-124 bpm, irregular rhythm, RR-28 cpm, BP-90/50mmHg, SPO2-97% in RA with raised JVP, hepatomegaly, ascites and basal crepitations. Child had clubbing (grade1) (Figure 1),

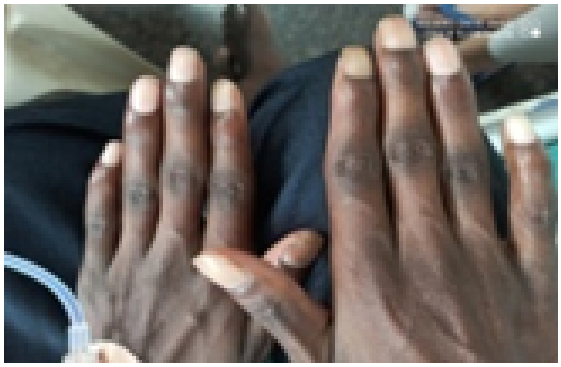

Fig 1. Clubbing

precordial bulge, gallop rhythm and no murmurs. He had brown, lusterless hair, woolly appearance (Figure 2), focal keratoderma over palms and soles (Figures 3 and 4) and few hyerpigmented atrophic patches over trunk. ECG showed – inverted T waves(V1-V3), QRS prolongation and complete RBBB (Figure 7). Echocardiography revealed-severe biventricular dysfunction with EF-15-20%, severe Mitral regurgitation, severe Tricuspid regurgitation and PAH (Figure 6). Patient was treated with diuretics, ß blockers and ACE inhibitors.

Discussion

Epidemiology and genetic substrate

Naxos disease is inherited as autosomal recessive pattern. The disease was first described by Protonotarios et al in families originating from the Greek island of Naxos. Apart from Naxos, affected families have been detected in other Greek Aegean islands, Turkey, Israel and Saudi Arabia. The prevalence of the disease in the Greek islands may be as high as 1:1000. A variety of Naxos disease, reported as Carvajal syndrome, has been described in families from India and Ecuador.[1]

Fig 2. Wooly appearance

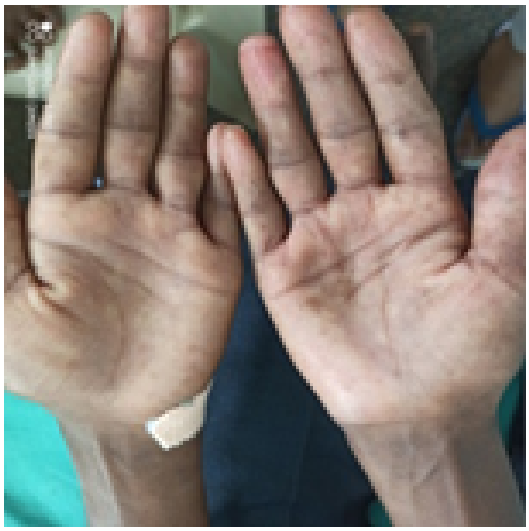

Fig 3. Focal keratoderma over palms

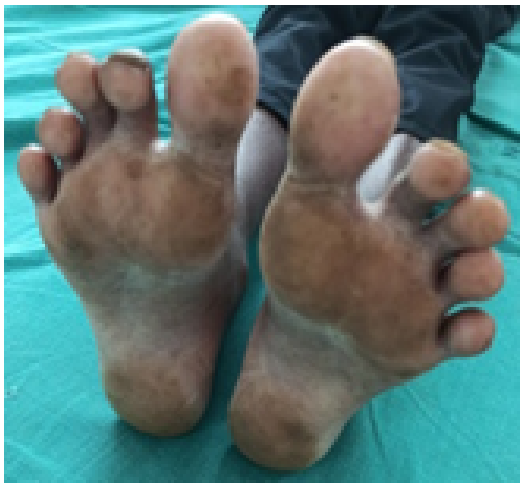

Fig 4. Focal keratoderma over soles

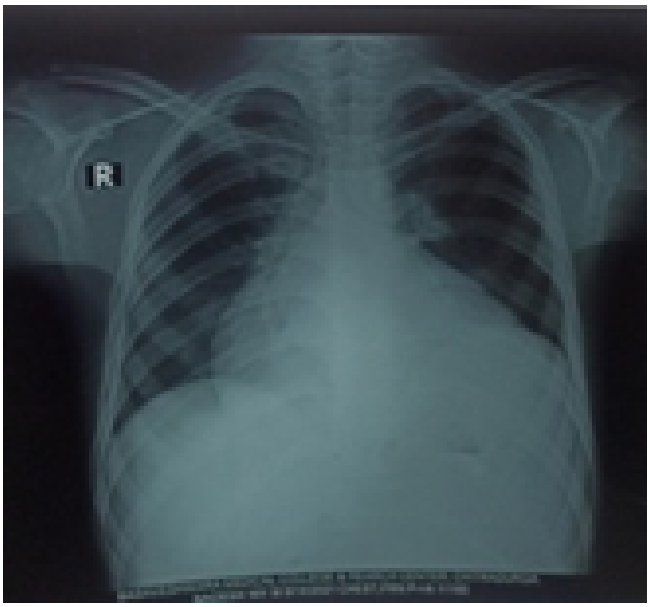

Fig 5. X-ray

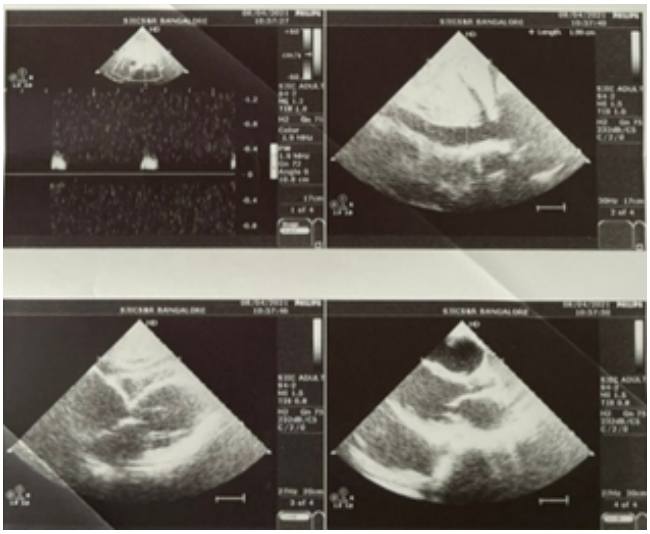

Fig 6. Sonography

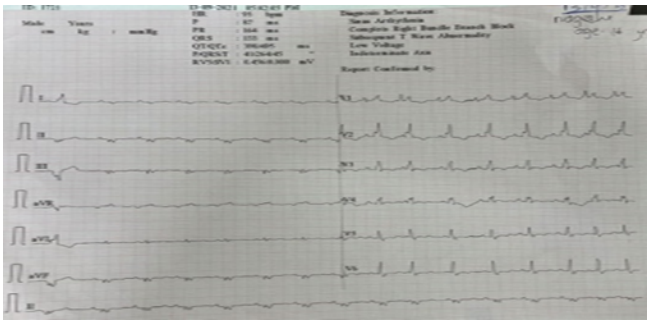

Fig 7. ECG

The genetic locus of Naxos disease lies in chromosome17q21 with mutation in gene encoding Plakoglobin (desmoprotein).[2] CARVAJAL Syndrome, a variant of Naxos, presenting with same cutaneous phenotype with predominant left ventricular involvement and early morbidity, is caused by a mutation in Desmoplakin gene mapping to chrm6p24.

Clinical presentation of Naxos disease

Naxos disease manifests with a typical phenotype including both cardiac and extracardiac characteristics.

Regarding Cardiac characteristics

This disease resembles ARV phenotype. Usually cardiac involvement occurs in adolescents and young adults. The symptomatic presentation is usually with syncope and/or sustained ventricular tachycardia of left bundle branch block configuration. Sudden death may be one of the manifestations of the disease. Echocardiography frequently portrays right ventricular dysfunction. In more detail, prominent dilation is often present along with hypokinesia and aneurysms that affect mainly the outflow tract, apex, and inferior wall of the right ventricle (Triangle of dysplasia). In a quarter of the cases, the left ventricle is also affected.

Extracardiac manifestations

Wooly and rough hair, commonly present from birth. As the child starts using hands and feet, develops diffuse palmoplantar keratoderma. Small arms and hands, short fingers, curved nails and hypo/oligodontia have also been reported in some cases.[3]

Pathophysiology and diagnostic criteria

Plakoglobin (γ-catenin) and desmoplakin are intracellular proteins anchoring desmosomes to desmin intermediate filaments. Defects in linking sites of these proteins can interrupt the contiguous chain of cell adhesion, particularly under conditions of increased mechanical stress or stretch, leading to detachment of myocytes at intercalated discs with progressive myocyte apoptosis. As the regeneration of cardiac myocytes is limited, fibrofatty replacement takes place and provides anatomic basis for progressive cardiac failure, arrythmias and sudden cardiac death.[4]

In the landmark paper Protonotarios et al., all patients were reported to have following ECG and Echo findings.

- **ECG —** Wide QRS and inverted T-waves in V1-V3 or in all precordial leads, while epsilon waves may also be present. An incomplete right bundle branch block may also be apparent, while the extrasystoles tend to manifest with an LBBB morphology. Flattened T-waves appear in the case of biventricular involvement.

- **ECHOCARDIOGRAPHY —** Dysfunction, hypokinesia and aneurysms are prominent.
- **HISTOLOGY —** Fibrofatty patterns are prominent
- **IMMUNOHISTOCHEMISTRY —** Signal of plakoglobin and connexin-43 in the intracellular junctions is diminished.

Diagnostic criteria for ARVC should be fulfilled (according to original task force criteria)

3 Major criteria

1. Dyskinetic RV wall diastolic out bulging
2. Epsilon wave in Lead V1
3. Sustained VT of LBBB morphology with superior axis

Treatment and Prevention

The primary goal is the prevention of sudden cardiac death.

- **Antiarrhythmic drugs** - sotalol and amiodarone, either alone or in combination with classical β-blockers-recurrences of episodes of sustained ventricular tachycardia.
- **Diuretics and angiotensin-converting enzyme (ACE) inhibitors** - congestive heart failure.
- **Heart transplantation** - is considered at the end stages. [5]

Children may need implantation of automatic cardioverter defibrillator to prevent arrhythmogenic attacks and sudden cardiac death.

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