CASE REPORT

Cardiac events in Costello syndrome: One case and a review of the literature

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Costello syndrome is a rare syndrome associated with de novo mutations in the HRAS gene. It is mostly revealed during in the first months of life by growth retardation, facial dysmorphic features, skin and cardiac abnormalities and subsequent cognitive deficit of varying severity. We report a case of Costello syndrome in a 3-month-old infant. The initial cardiac investigations were normal except frequent premature atrial complexes. After few months, worsening arrhythmia with bursts of ventricular tachycardia were noted as well as the secondary progressive obstructive left ventricular hypertrophic cardiomyopathy (HCM).

Cardiac involvement is determinant for the prognosis of Costello syndrome. It frequently consists of hypertrophic cardiomyopathy (one third of patients), with involvement of the left ventricle in half of the cases. It is often asymmetrical and associated with obstruction of the outflow recalling family hypertrophic cardiomyopathy. The natural history of HCM in Costello syndrome and its management remains poorly known because of paucity of reported cases. Progression of the HCM can be very rapid like the reported case. On the other hand, the spontaneous regression of the HCM in some patients has been reported. In addition, cardiac threatening arrhythmias may be noted. So that, cardiac assessment and monitoring with regular echocardiography and electrocardiogram follow up is mandatory.

Introduction

Costello syndrome is a rare syndrome associated with de novo mutations in the HRAS gene. The prevalence of this syndrome is unknown, but about 250 cases have been reported in the literature [1]. We report the case of an infant with Costello syndrome with severe cardiac events and we present a brief review of literature on the characteristics of cardiac involvement in this syndrome.

Observation

We report the case of a 03 month old male infant. His parents were concerned about swallowing disorders with loss of weight of 900 g in 1 month. The medical history revealed severe hydramnios, macrosomia with a birth weight of 4700 g and neonatal hypoglycemia and hypocalcemia. The infant had a weight of 4300 g at his first presentation. Physical examination revealed facial dysmorphism suggestive of Costello syndrome with macrocephaly (head circumference of

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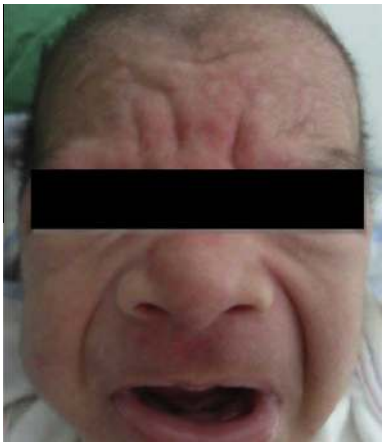

Figure 1. Dysmorphic features suggestive of Costello's syndrome.

41.5 cm so −3 SD), epicanthus, strabismus, flattened nose, low-set ears, macroglossia and short neck (Fig. 1). The infant also had skin abnormalities and hair and nail characteristics of Costello syndrome: Cutis laxa (Figs. 2a and b), deep folds of the palms and soles (Fig. 3a and b), laxity of small joints of the hand and axial hypotonia. Psychomotor development and growth of our patient were marked by poor gain of weight, short stature, delayed psychomotor acquisitions and poor coordination sucking – swallowing.

A genetic study confirmed the diagnosis of Costello syndrome

On cardiovascular routine examination, the heart rate was around 140 beats per min. Blood pressure was 80/40 mm Hg and cardiac auscultation was normal. The femoral pulses were well felt and there was no sign of heart failure. The electrocardiogram showed a regular sinus rhythm with some premature ventricular contractions (PVCs). The initial echocardiogram was normal. In particular, there was no evidence for a cardiomyopathy or septal defect and the heart valves were thin and healthy. The ECG Holter monitoring showed frequent PVCs sometimes in doublets associated to few bursts of premature atrial complexes. The infant was then started on beta blockers and close monitoring was recommended.

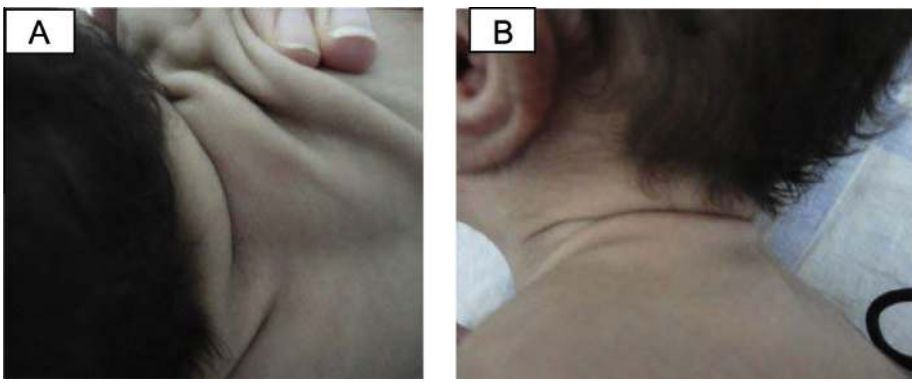

Figure 2. (A and B) : Cutis Laxa features.

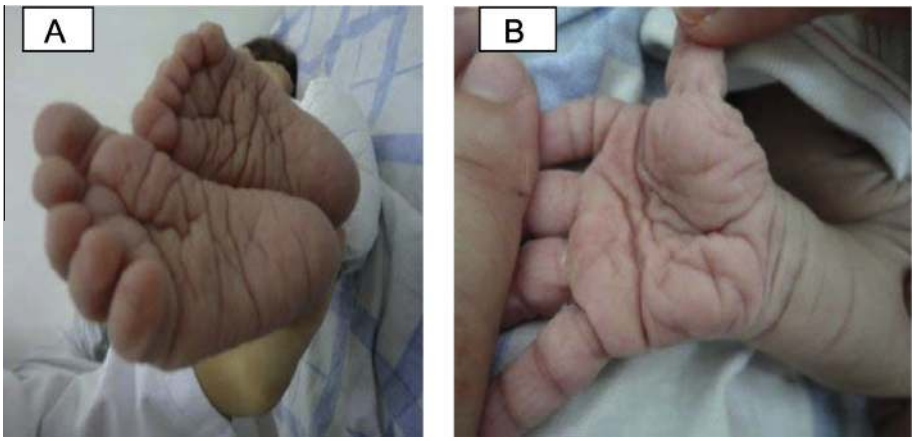

Figure 3. (A and B): Deep skin folds at the soles of the feet (A) and palms (B).

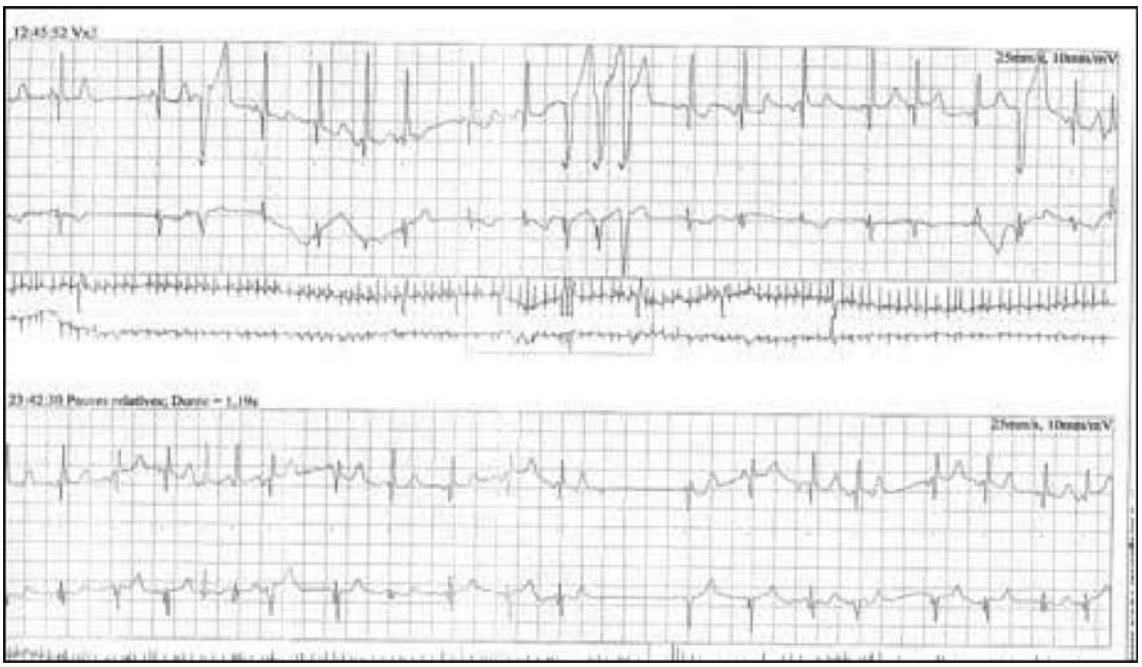

Figure 4. Repetitive premature ventricular complexes.

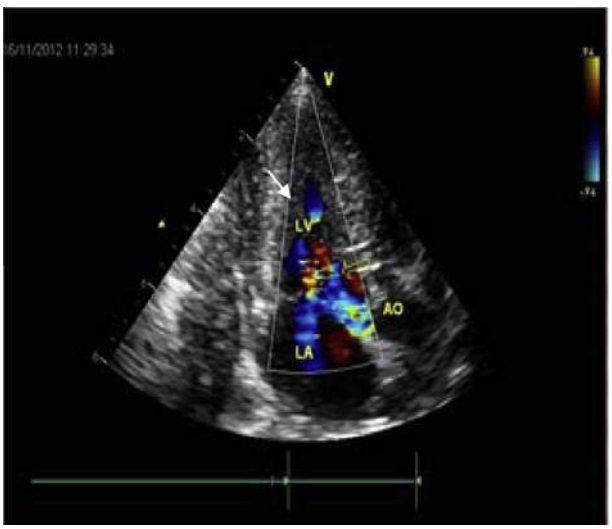

Figure 5. Apical view showing moderate mitral regurgitation and acceleration of the flow over the sub aortic region.

Three months later, echocardiographic study showed an asymmetric non obstructive hypertrophic cardiomyopathy involving especially the basal part of the ventricular septum measured at 9 mm. There was no left ventricular outflow obstruction or mitral regurgitation. Left ventricular function was preserved and pulmonary pressures were normal. The ECG Holter monitoring objectified repetitive PVCs in doublets and triplets with ventricular tachycardia bursts (Fig. 4). We decided to add amiodarone to the beta blocker treatment.

The evolution was marked by the disappearance of ventricular tachycardia bursts, and a scarcity of PVCs. The infant was asymptomatic cardiac wise and swallowing disorders are relatively improved, thanks to a rehabilitation of swallowing. However, echocardiographic assessment done three months later showed a worsening of HCM with septal thickness of 10 mm, thickened mitral valve with onset of moderate mitral regurgitation, as well as a left ventricular outflow tract obstruction with a peak gradient of 40 mm Hg measured 2 months later at 64 mm Hg (Figs. 5 and 6).

Discussion

Costello syndrome was first described in 1971 by Costello [2]. The gene responsible for this syndrome is the HRAS gene [3]. Diagnosis is mainly clinical. In the series published by Lin and al about 61 genetically confirmed cases of Costello syndrome, the average age at diagnosis was 4.2 years. The diagnosis was made before the age of 1 year in one third of cases [4]. Clinical presentation consists on facial dysmorphism, growth retardation associated with severe psychomotor retardation and feeding difficulties [5]. A notion of polyhydramnios during pregnancy, macrosomia and neonatal hypoglycemia are often found [6]. Prognosis is dependent on frequent develop-

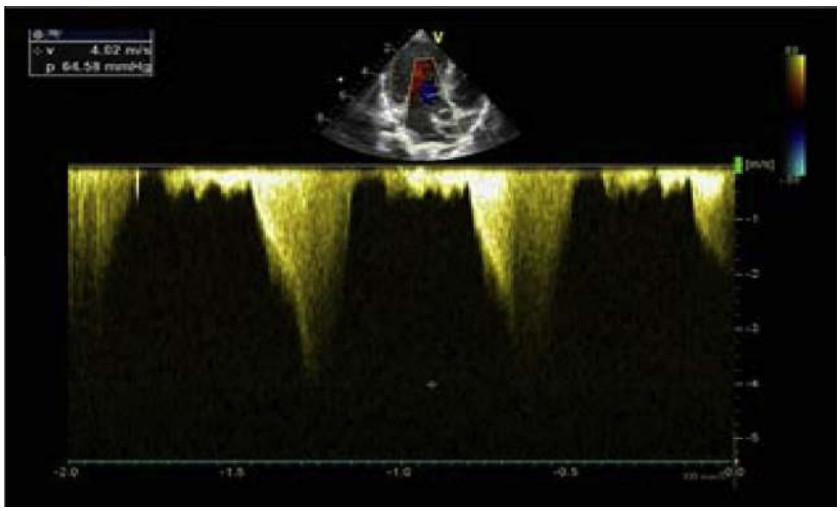

Figure 6. Peak gradient of 64 mm Hg over the left ventricular outflow tract.

ment of tumors, essentially rhabdosarcomes neuroblastoma on one hand and on the cardiac involvement on the other hand [4]. The most common reported heart lesions are pulmonary stenosis, hypertrophic cardiomyopathy, cardiac arrhythmias, atrial or ventricular septal defects (44%) and congenital mitral valve abnormalities [7]. Dysmorphia and cardiac involvement of Costello syndrome are similar to those of Noonan syndrome, cardio-facial-cutaneous syndrome (CFC) and LEOPARD syndrome. These syndromes are due to mutations in genes that encode proteins involved in the intracellular cascade of RAS/mitogen-activated protein kinase (MAPK). They are also called ''RASopathies'' [3].

The prevalence of HCM in Costello syndrome varies from 20% to 61% depending on the series [4,7]. In the series of Swiwik et al. [7], the age of discovery of the HCM ranged from 5 months to 20 years. Similarly, Lin et al. [4] noticed that the diagnosis of HCM is not always done at birth. Indeed, some patients develop HCM later, as is the case of our patient. This could be related to myocardial accumulation of metabolites over time [8]. Regular echocardiographic monitoring is necessary because for the possibility of rapidly evolving forms of HCM as in the case of our patient.

HCM in Costello syndrome is similar to familial forms of HCM. Symptoms usually described are dyspnea, angina, syncope, arrhythmias and sudden death. The hypertrophy of basal part of the ventricular septum is the most common [9]. Severe hypertrophy and left ventricular out flow obstruction and may be cause of dyspnea or angina on exertion. Life-threatening ventricular arrhythmias are possible.

At histological analysis, hypertrophy, myocyte disorganization and fibrosis, which represent the anatomical substrate of ventricular arrhythmias, were identified in the HCM Costello syndrome [8].

Resolution or significant spontaneous regression of the septal hypertrophy has been interpreted as a phenomenon of widespread remodeling leading to raise the hypothesis that the HCM associated with Costello syndrome is not a static disease [4]. Moreover, a rapidly fatal evolution with a rapid enhancement of the left ventricular gradient and occurrence of heart failure signs has been reported in the literature [10].

To improve the quality of life of these patients, medical intervention and / or surgery may be necessary to reduce the degree of obstruction and reduce complications such as arrhythmias [11].

Supraventricular tachycardia, especially atrial tachycardia is frequently associated with Costello syndrome (up to one third of patients). The first cases of Costello syndrome associated to supraventricular rhythm disturbances have been reported in 1993 [12]. Then Siwik et al. [7] described the cardiac manifestations of Costello syndrome in 30 patients, 18% had tachyarrhythmias. It was ectopic atrial tachycardia, supraventricular tachycardia of unspecified mechanism and a case of flutter. In the series published by Lin et al. [13], one third of children had arrhythmias, 74% in type of atrial tachycardia. The other children had ventricular arrhythmias in type of premature ventricular complexes or well tolerated neonatal ventricular tachycardia. Our infant had impaired ventricular excitability with bursts of ventricular tachycardia, which have well resolved on anti arrhythmia drugs.

Conclusion

Costello syndrome is a rare genetic syndrome. Clinical expertise and molecular study allow the diagnosis of this disease. Cardiac involvement, particularly hypertrophic cardiomyopathy and rhythm disorders, alters the prognosis. Their possible rapidly fatal progression imposes a close cardiac rhythm monitoring and echocardiography follow up.

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