Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria

CASE REPORT

Costello syndrome: Case report and review of diagnostic approach

Ana Paula da Rosa Pereira[1], Sabrine Teixeira Ferraz Grunewald[2]

Keywords:
cardiac arrhytmias, cardiomyopathy, hypertrophic, Costello syndrome.

Abstract

Objective: Costello syndrome is an autosomal dominant disorder caused by mutations in HRAS gene, which produces a protein involved in controlling cell division and growth. It is a very rare clinical condition, with about 200 to 300 confirmed cases worldwide. One of the most serious manifestations is cardiac arrhythmia, potentially fatal. **Objective:** We propose an account of a clinically diagnosed case like Costello syndrome, and discuss the management of associated cardiac arrhythmia. **Methods:** Case report after chart review, and review of literature. **Results:** An infant of female, 1 year and 3 months old, with clinical diagnosis of Costello syndrome, was admitted for evaluation of cardiac arrhythmia. She presented hypertrophic cardiomyopathy in echocardiography,. The Holter exam revealed atrial and supraventricular tachycardia with aberrance, unstable left atrium, refractory cardiac arrhythmia and blocked atrial premature beats. It was decided to start amiodarone 5mg/kg/day and captopril 1mg/kg/day, with reassessment after two weeks of treatment. There was improvement in cardiac auscultation, but she maintained the ECG pattern. Due to the general prognosis of the patient, it was decided by outpatient treatment, and there was clinical and electrocardiographic improvement. **Conclusion:** There are no specific guidelines for the treatment of cardiac arrhythmias in Costello syndrome. Patients who develop this complication have a poorer prognosis, and it is needed to decide, together with the family, the best conduct.

[1] Pediatrician. Ex- resident. Hospital Universitário da Universidade Federal de Juiz de Fora, Juiz de Fora, MG, Brazil.
[2] Pediatric haematologist and haemoterapist . Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto - Universidade de São Paulo. MsC. Biologic Sciences. Universidade Federal de Juiz de Fora, Juiz de Fora, MG, Brazil.

Correspondence to:
Ana Paula Rosa Pereira.
University Hospital affiliated to the Federal University of Juiz de Fora. Rua Catulo Breviglieri, s/nº, Santa Catarina, Juiz de Fora, MG, Brazil. CEP: 36036-110.

Residência Pediátrica 2016;6(3):141-144.

INTRODUCTION

Costello syndrome is an autosomal dominant pathology first described in 1977, and caused by mutations in the HRAS gene, located on chromosome 11p15[1]. This gene encodes a protein involved in control of cell growth and division, and its mutation may be observed in 90% of individuals with Costello syndrome clinical features[2,3]. It is a very rare clinical condition, with approximately 200 to 300 confirmed cases worldwide[2]. Most known cases occurs from new mutations without a family history of similar cases, but the inheritance pattern seems to be autosomal dominant[2].

Costello syndrome is a complex developmental disorder, involving craniofacial anomalies, low body mass gain, delayed development, and cardiac and skeletal abnormalities[3,4]. Since its first description, Costello syndrome has been diagnosed in several patients, and it has been gaining prominence in the literature due to the observation of tendencies for the development of malign tumors, in particular rhabdomyosarcoma, ganglioneuroblastoma, and bladder tumors[3,5].

Costello syndrome signs and symptoms may significantly overlap cardiofaciocutaneous and Noonan syndrom, which are also genetic conditions. Although it may be difficult to differentiate these conditions, especially in young children, the distinction can be made based on symptoms patterns that appear later in childhood. Mutation detection by molecular biology techniques is the gold standard for Costello syndrome diagnosis. However, because these techniques are not widely available, guidelines for its clinical diagnosis were established[6].

Here, we report a case clinically diagnosed as Costello syndrome and discussed the management of cardiac arrhythmia, one of its life threatening complications. In addition, we present a brief review of the literature about this pathological condition.

CASE REPORT

A female infant, 1 year and 3 months old, with clinical diagnosis of Costello syndrome, was hospitalized in order to treat a cardiac arrhythmia in the Pediatric Infirmary at the University Hospital affiliated to the Federal University of Juiz de Fora after an evaluation in the Pediatric Cardiology Department.

Her previous history indicated that she was born full-term at 39 weeks with 3,270 grams, which is an appropriate body mass for her gestational age, and without prenatal complications. Parents are not related, and there was no family history of genetic malformation. After being released from the hospital, she was referred to a geneticist for an evaluation due to dimorphisms and was further clinically diagnosed with Costello syndrome. No abnormalities were found in her karyotype examination.

Since her first month of life, she had difficulty in gaining weight and stature, and she had been previously hospitalized to receive enteral nutrition. Currently, she weighs 5,140 grams and has 62 cm of height, which are both below the Z-score -3. Skin with deep plantar and palmar creases, full lips, large mouth, ogival palate, absence of tooth eruption; fine and curly hair, and sacrococcygeal hemangioma (Figure 1) were observed during examination. In the development evaluation, she could briefly sit without support and but could not stand up on her own. Also, she did not talk, although she showed to have a good social interaction with her mother.

Patient's cardiac auscultation was irregular, with a pulse frequency of 105 bpm. The electrocardiogram detected an important arrhythmia (Figure 2). The echocardiogram revealed a hypertrophic cardiomyopathy, and the Holter monitor showed an atrial and supraventricular tachycardia with aberrancies, in which the left atrium was unstable, cardiac arrhythmia was refractory, and atria extra systoles were blocked.

We opted for the initial treatment with amiodarone at 5 mg/kg/day and captopril at 1 mg/kg/day, and reassessment after two weeks of treatment. During this period, the child remained hospitalized, with high calorie infant formula administration via nasogastric tube to improve gain mass.

Reexamination by the cardiologist showed that arrhythmia improved on auscultation, but the electrocardiographic pattern was unchanged. Based on that, medications and dosages were maintained and she was discharged and referred to ambulatory follow-up. The child remained hospitalized for 30 days, during which she gained approximately 500 grams of body mass. Because of her coarse face, a differential diagnostic test for mucopolysaccharidosis was performed, which turned out to be negative.

During ambulatory follow-up with a pediatric cardiologist, the patient clinical condition evolved, presenting a progressive improvement of the cardiac arrhythmia. Approximately one year after being released from the hospital, her electrocardiogram showed sinus rhythm. The child still does follow-ups, without further complications.

DISCUSSION

Costello syndrome clinical manifestations comprise, in particular, facial features, difficulty in gaining weight and stature, and cardiac alterations[7]. According to their frequency and specificity, these manifestations were used as basis for clinical diagnosis guidelines of this syndrome (Chart 1). The reported case patient matches all major criteria and the three unique features of greater specificity, which makes a very probable diagnosis.

Feeding difficulties, poor suction power, and insufficient weight gain are frequent clinical manifestations of this syndrome, and children may be born either at full-term with appropriate weight or be premature with low weight[3]. The need for an alternative feed administration must be evaluated. The neuropsychomotor development delay can be highly variable, and most patients have significant intellectual impairment[7,8], which makes early stimulation essential.

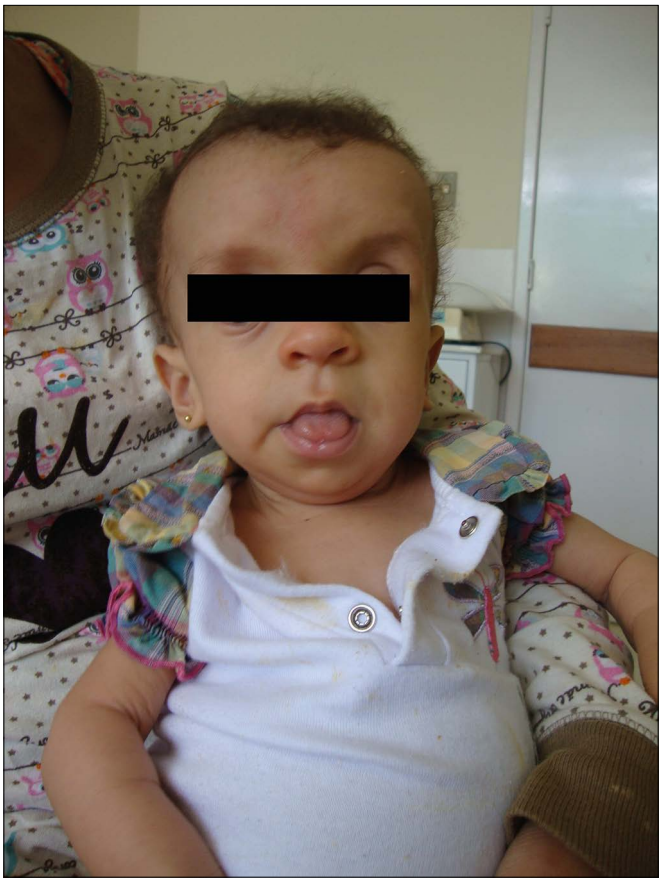

Figure 1. Some of the typical facial features of Costello syndrome. Outstanding features include the large mouth with full lips and absence of tooth eruption, the fine and curly hair, and a relative macrocephaly.

Main facial features include absolute or relative macrocephaly, frizzy and sparse hair, epicanthic fold, strabismus, low nasal bridge, large mouth with thick lips, and thick earlobes, which leads to a rough facial impression[5]. Muscle-skeletal manifestations include inguinal hernia, joint hypermobility, feet positioning abnormalities, delayed bone age, and calcaneal tendon thickening. Often there are redundant skin on the neck, hands and feet, with deep furrows, as well as the presence of papillomas[2,5].

Arrhythmias are reported in at least one third of patients, and it is often associated with hypertrophic cardiomyopathy[1]. However, there are no established guidelines to treat these cardiologic conditions. It is recommended a pediatric cardiologist evaluation on children with suspicion or confirmed Costello syndrome at least annually. In these consultations, electrocardiogram, echocardiogram, and Holter monitoring should be performed[1,7]. The identification of severe arrhythmia worsens the prognosis and it is associated to lower survival[1]. Congenital heart defects are also common, including valvular stenosis, septum defects, in addition to hypertrophic cardiomyopathy[5].

In the case reported, infant showed severe but asymptomatic arrhythmia. It was not possible to ideally control the heart rate by medication administration. However, considering her prognosis and after conversations with her family, infant was released from hospital and referred to frequently ambulatory follow up. One year after being released from the hospital, patient remained asymptomatic, with improvements in weight gain, suction power and development. At this time, electrocardiographic test revealed a sinus cardiac rhythm.

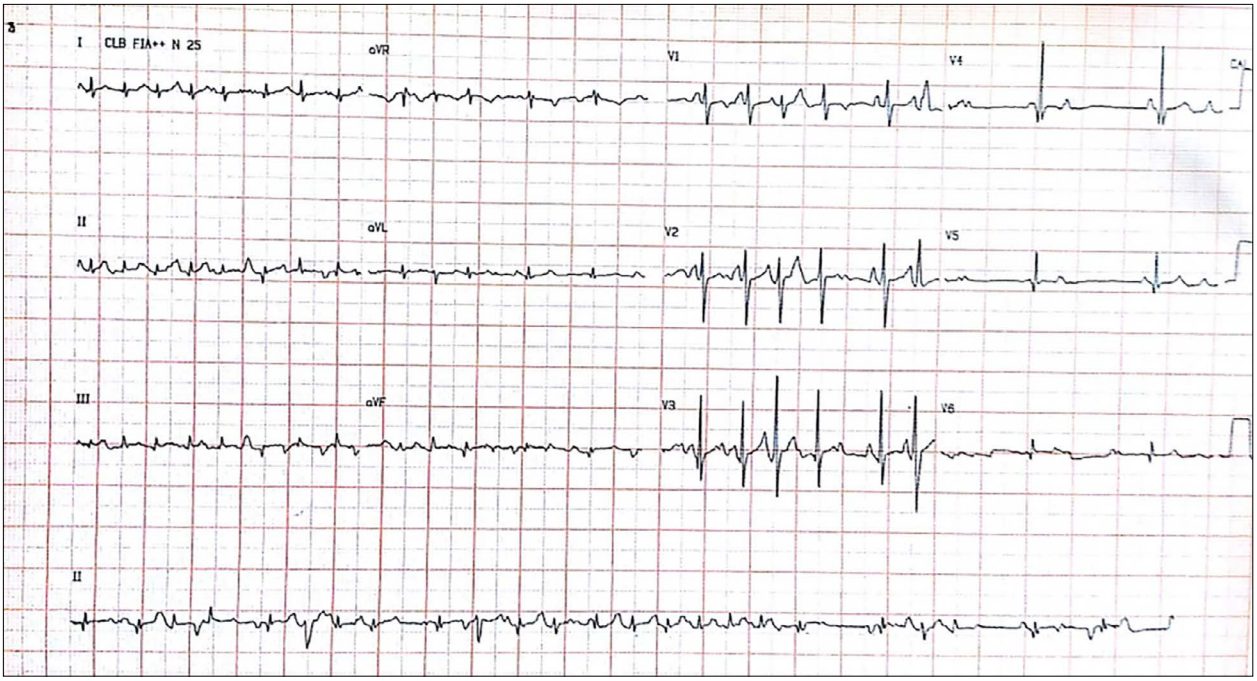

Figure 2. Electrocardiogram examination showing a complex cardiac arrhythmia.

Chart 1. Costello syndrome clinical manifestations. Percentages represent the estimated frequency of each feature. Items in italics when combined with major features increase diagnosis specificity. Adapted from Costello Syndrome Guidelines for Clinical Diagnosis.

Major Features	Unique Features	Other Features
Dysphagia/feeding difficulty/need for gastrostomy (95%)	*Congenital heart diseases (65%): pulmonary stenosis (20%), hypertrophic cardiomyopathy (40%), atrial tachycardia (30%)*	Polyhydramnios (62%)
Postnatal short stature (97%)	*Benign (44%) and malign (16%) tumors*	Birth body mass alterations (> 50%)
Typical facial features (98%)	*Typical facial features with large mouth (78%)*	Hernias (50%)
Thick lips (95%)	Elastic skin with hyperpigmentation	Visual abnormalities - ptosis, strabismus
Loose skin (94%)	Kyphoscoliosis	
Abnormally deep palmar grooves (99%)	Captivating personality	
Development delay (100%)	Curly hair	
	Normal head circumference	

Because Costello syndrome prevalence is unknown, authors have suggested that it may be misdiagnosed or even confused with Noonan syndrome[7]. This syndrome requires further research, so that the pathophysiology of its manifestations can be better understood and with development of more personalized therapies.

CONCLUSIONS

Costello syndrome is a rare pathological disease with genetic etiology and variable phenotype, in which the molecular diagnostics is often unavailable in clinic practice. Thus, pediatricians need to be attentive to its clinical manifestations, so suspect cases are detected and appropriate follow-up is provided. Patients whose condition progresses have a worse prognosis and the best treatment strategy needs to be decided and along with their family.

REFERENCES

1. U.S. National Library of Medicine. Costello syndrome [Internet]. [citado 2015 Jun 7]. Disponível em: https://ghr.nlm.nih.gov/condition/costello-syndrome
2. Gripp KW, Stabley DL, Nicholson L, Hoffman JD, Sol-Church K. Somatic mosaicism for an HRAS mutation causes Costello syndrome. Am J Med Genet A. 2006;140(20):2163-9. PMID: 16969868 DOI: http://dx.doi.org/10.1002/ajmg.a.31456
3. Aoki Y, Niihori T, Kawame H, Kurosawa K, Ohashi H, Tanaka Y, et al. Germline mutations in HRAS proto-oncogene cause Costello syndrome. Nat Genet. 2005;37(10):1038-40. PMID: 16170316 DOI: http://dx.doi.org/10.1038/ng1641
4. Estep AL, Tidyman WE, Teitell MA, Cotter PD, Rauen KA. HRAS mutations in Costello syndrome: detection of constitutional activating mutations in codon 12 and 13 and loss of wild-type allele in malignancy. Am J Med Genet A. 2006;140(1):8-16. PMID: 16372351 DOI: http://dx.doi.org/10.1002/ajmg.a.31078
5. Hennekam RC. Costello syndrome: an overview. Am J Med Genet C Semin Med Genet. 2003;117C(1):42-8. PMID: 12561057 DOI: http://dx.doi.org/10.1002/ajmg.c.10019
6. Costello Sydrome Family Network. Costello Syndrome Guidelines for Clinical Diagnosis [Internet]. [citado 2015 Jun 7]. Disponível em: http://costellokids.com/sites/default/files/vp_cs_trifold_122205b_english.pdf
7. Siwik ES, Zahka KG, Wiesner GL, Limwongse C. Cardiac disease in Costello syndrome. Pediatrics. 1998;101(4 Pt 1):706-9.
8. Axelrad ME, Glidden R, Nicholson L, Gripp KW. Adaptive skills, cognitive, and behavioral characteristics of Costello syndrome. Am J Med Genet A. 2004;128A(4):396-400. PMID: 15264285 DOI: http://dx.doi.org/10.1002/ajmg.a.30140