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Brief Report

Medical and surgical perspectives of cardiac hypertrophy in Costello syndrome

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Abstract We describe our experience with 2 patients having Costello syndrome, aged 11 and 36 months, who suffered systolic anterior motion of the aortic leaflet of the mitral valve and obstructive cardiac hypertrophy requiring surgery, comparing their cardiac characteristics to those described previously. We conclude that the heterogeneous nature of the cardiac hypertrophy in this syndrome can be considered and managed as the sum of a diffuse hypertrophy accessible to beta-blockade, and an asymmetric hypertrophy accessible to surgical myomectomy.

Keywords: Beta-blockers; hypertrophic cardiomyopathy; genetic syndrome; subaortic stenosis; supraventricular tachycardia; surgical myomectomy

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COSTELLO SYNDROME IS A RARE GENETIC DISORDER, initially described in 1971,[1] caused by activating germline mutations in RAS proto-oncogenes, and characterized by prenatally increased growth, postnatal growth retardation, coarse facies, loose skin resembling cutis laxa, developmental delay, cardiac abnormalities, and an outgoing, friendly behaviour.[2] Cardiac abnormalities are found in up to three-quarters of the patients,[3,4] and can be summarised in terms of cardiovascular malformations, cardiac hypertrophy, and disturbances of rhythm, each occurring in approximately one-third of patients with cardiac involvement.[5] Contrary to the clinical cardiac phenotype, the management of these cardiac abnormalities is very poorly documented, according to the first International Costello Syndrome Research Symposium,[1] must represent one of the major research directions. Our objective in this report, therefore, is to describe 2 new children with Costello syndrome complicated with obstructive cardiac hypertrophy requiring surgery, comparing their cardiac anatomical characteristics as revealed by ultrasound to those previously described, and based on these findings, to propose a combined medical and surgical approach to treatment.

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Case Reports

We summarise the gender, age, and cardiac abnormalities of our patients in Table 1. The features of their medical and surgical management is summarised in Table 2.

Discussion

We report here our experience with 2 children diagnosed with Costello syndrome complicated with diffuse and asymmetric hypertrophic obstructive cardiomyopathy. The asymmetric component of the septal htpertrophy was successfully treated with surgical myomectomy, while we treated the diffuse non-obstructive component using beta-blockers.

The absence of involvement of siblings in either case supports the proposal that Costello syndrome is

Table 1. Demographic and cardiac abnormalities in our patients.

	First patient	Second patient
Gender	Female	Female
Birth	At term by emergency Caesaerian section due to respiratory distress	At term by vaginal delivery
Birth weight	3850 grams	3900 grams
Age at diagnosis of Costello syndrome	12 months	1 month
Symptoms for Costello syndrome	Laryngomalacia, growth retardation, dysmorphic features (coarse facies, depressed nasal bridge, sparse hair, thick lips and low set ears), loose skin with excessive pigmentation, hyperlaxity, nasal papillomata and delayed psychomotor development with hypotonia	Growth failure, dysmorphic features, cutis laxa, laryngomalacia and cardiac abnormalities
Parental consanguinity or recurrence in siblings	No	No
Age at recognition of cardiac abnormalities	39 months	1 month
Cardiac abnormalities	• Diffuse cardiac hypertrophy (diastolic 20-mm interventricular septum) • Obstructive asymmetric septal thickening on the left side (subaortic mean pressure gradient of 100 mmHg) • Mitral valve systolic anterior motion • Moderate mitral regurgitation related to abnormal mitral valve cords and mitral valve systolic anterior motion	• Diffuse cardiac hypertrophy (diastolic 9-mm interventricular septum) • Obstructive asymmetric septal thickening on the left side (subaortic mean pressure gradient of 60 mmHg) • Mitral valve systolic anterior motion • 16 mm-diameter hole in the floor of the oval fossa • Moderate mitral regurgitation related only to mitral valvar systolic anterior motion
Electrocardiogram	Normal sinus rythm	Normal sinus rythm

caused by sporadic mutations.[6] The extracardiac findings in our children are consistent with those noted in the first reported cases, and with those emphasised by subsequent reviews.[1–3] As for the cardiac abnormalities, previous reports show that the combination of cardiac hypertrophy, atrial tachycardia, and mild pulmonary stenosis is characterisric, but not pathognomonic, for the syndrome.[1] An extensive review of the literature showed that a cardiovascular malformation is present in almost one-third of patients with the syndrome, with almost half of these patients having pulmonary stenosis.[5] Neither of our patients, however, had pulmonary stenosis. This is consistent with recent genetic studies showing that the cardiovascular malformations, especially pulmonary stenosis associated with an interatrial communication across the oval fossa, are significantly more common in the cardio-facial-cutaneous syndrome with BRAF or MEK1 mutations than in Costello syndrome.[1,7] Abnormal leaflets of the mitral valve had been described as myxomatous, redundant, or thick in 6 patients with Costello syndrome,[8] whereas our first patient had abnormally tendinous cords supporting normal mitral valvar leaflets. The presence of a supraventricular tachycardia in our second patient is also consistent with previous experience, this being the disturbance of rhythm noted in three-quarters of patients with the syndrome. The tachycardia noted in our patient, however, is probably not only due to the syndrome, but rather to perioperative stress. There are 2 reasons supporting this presumption: first the abnormal rhythm was neither chaotic, multi-focal nor ectopic, as would be expected for Costello syndrome, and second, it did not become manifest until after surgical relief of the cardiac hypertrophy, a happening which, to the best of our knowledge, is thus far unique.

When we compare the characteristics of cardiac hypertrophy in our patients with other reported experience, we find that this purportedly classical feature of Costello syndrome is very heterogeneous in terms of its anatomical distribution, onset, natural history, and prognosis.

When considering the anatomical distribution, asymmetric septal thickening along with anterior systolic motion of the aortic leaflet of the mitral

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Table 2. Characteristics of the medical and surgical management.

	First patient	Second patient
Age and weight at surgery	41 months; 11 kgs	11 month; 8 kgs
Surgical procedure	• Transaortic myomectomy • Resection of abnormal mitral valvar cords	• Transaortic myomectomy • Closure of atrial septal defect
Time of cardiopulmonary bypass and aortic cross-clamping	96/72 minutes	83/55 minutes
Complications	Anaphylactic shock to protamine	1) postoperative supraventricular tachycardia treated by amiodarone for 6 months 2) bilateral pleural effusion 3) Haemophilus pulmonary infection
Time of intubation and intensive care	2/3 days	7/12 days
Follow-up	5 years	4 years
Outcomes	• Persistant diffuse symetric cardiac hypertrophy requiring beta-blockers • No residual or recurrent subaortic stenosis • No mitral valve systolic anterior motion • No mitral regurgitation	• Persistant diffuse symetric cardiac hypertrophy requiring beta-blockers • No residual or recurrent subaortic stenosis • No mitral valve systolic anterior motion • No mitral regurgitation • No atrial septal defect • No disturbances of rhythm or conduction
Use of beta-blockers	Postoperative	Preoperative and Postoperative

valve is most characteristic.[5] Both of our patients, however, presented more complex patterns of hypertrophy, which at the same time was diffuse and non-obstructive, involving both ventricles, and asymmetric and obstructive, involving the subaortic left ventricular outflow tract.

With regard to onset, the hypertrophy is said to appear between the ages of 5 months and 20 years.[4] Follow-up of the original patients described by Costello,[2] nonetheless, showed hypertrophy becoming evident at the age of 27 years. The early occurence of cardiac hypertrophy in our second patient confirms that hypertrophy can also be found in neonates with the syndrome.[5]

When considering natural history, then contrary to the data presented in the extensive review,[5] the evolution of myocardial hypertrophy in both our patients was not in keeping with its phenotypic progression.[5]

Prognosis can be sometimes excellent, as in both our patients, but is sometimes fatal.[9,10] On the basis of this complex anatomical, evolutive, and prognostic heterogeneity, we believe that the medical and surgical teams should treat patients with the syndrome on an individual basis.

In this respect, it was the diffuse and asymmetric hypertrophic cardiomyopathy encountered in our patients that accounted for the decreased left ventricular compliance, subaortic stenosis, and mitral regurgitation. Only the latter 2 elements were accessible to surgical septal myomectomy. Such myomectomy did not improve the diffuse hypertrophy that persisted in both patients, but it prevented any recurrence of subaortic stenosis as judged at mid-term follow-up. Thus, we suggest that the heterogeneous cardiac hypertrophy encountered in Costello syndrome should be managed, on the one hand, as a diffuse feature accessible to a medical treatment by beta-blockade, but on the other hand as asymmetric hypertrophy accessible to surgery.

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