Published in final edited form as:
Prenat Diagn. 2009 July ; 29(7): 682–690. doi:10.1002/pd.2276.

Prenatal features of Costello syndrome: Ultrasonographic findings and atrial tachycardia

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Abstract

Objective—Delineate prenatal features of Costello syndrome (caused by *HRAS* mutations) which consists of mental retardation, facial, cardiovascular, skin, and musculoskeletal anomalies, and tumor predisposition.

Methods—Literature and new cases classified as Group I (pre-*HRAS*), Group II (*HRAS* confirmed), and Group III (*HRAS* confirmed in natural history study, plus three contributed cases).

Results—Polyhydramnios occurred in most (mean 79%) pregnancies of cases in Groups I (98), II (107), and III (17), advanced paternal age and prematurity were noted in approximately half. Less frequent were nuchal thickening, ascites, shortened long bones, abnormal hand posture, ventriculomegaly, macrosomia, and macrocephaly. Fetal arrhythmia occurred in 9 cases (6 supraventricular or unspecified tachycardia, 1 unspecified arrhythmia, 2 premature atrial contractions, PACs); excluding 3 new cases and 2 with PACs, the estimated prenatal frequency is 4/222 (2%).

Conclusion—Costello syndrome can be suspected prenatally when polyhydramnios is accompanied by nuchal thickening, hydrops, shortened long bones, abnormal hand posture, ventriculomegaly, large size, and macrocephaly, and especially fetal atrial tachycardia.

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Consideration should be given for timely prenatal diagnostic studies for confirmative *HRAS* gene mutations, and for maternal treatment of serious fetal arrhythmia.

Keywords

chaotic atrial rhythm; chaotic atrial tachycardia; Costello syndrome; fetal arrhythmia; *HRAS* gene; polyhydramnios; prenatal ultrasound; supraventricular tachycardia

INTRODUCTION

Costello syndrome typically presents with polyhydramnios, hypotonia and edema, accompanied by failure to thrive, short stature, neurodevelopmental and musculoskeletal problems and an approximate 15% risk for malignant tumors (Gripp, 2005; Gripp and Lin, 2006). There is relative macrocephaly, epicanthal folds, a wide nasal bridge, short nose, full lips, large mouth, nasal papillomata, wrist deviation, deep palmar and plantar creases, and loose skin. Cardiac manifestations include hypertrophic cardiomyopathy, pulmonic stenosis, and arrhythmias (Lin *et al.*, 2002; Gripp *et al*, 2006). Costello syndrome overlaps with other syndromes of the Ras/MAPK pathway, especially Noonan syndrome (Quezada and Gripp, 2007). *HRAS* is considered the single etiologic gene for Costello syndrome (Aoki *et al*, 2005; Kerr *et al*. 2008). Somatic mosaicism has been reported (Gripp *et al.*, 2007; Sol-Church *et al.*, 2009). The purpose of our study was to better characterize the prenatal features of Costello syndrome.

PATIENTS

CASE 1

This male, born to a 29-year-old G5 mother and 40-year-old father, had a 28 week prenatal ultrasound showing macrocephaly, significant ascites, and supraventricular tachycardia (SVT) (fetal heart rate 200–230 beats per minute, bpm). Maternal treatment with intravenous digoxin and flecainide suppressed the fetal SVT and reduced the ascites. At 34 weeks, the fetal heart rate was 140–150 bpm with frequent premature atrial contractions (PACs). Ultrasound at 35 weeks showed normal sinus rhythm, shortened femurs (4 weeks < gestational age), macrocephaly (5 weeks > gestational age) with appropriate ventricular and cerebellum size. At 36 weeks, this hypotonic male was delivered by spontaneous vaginal delivery in moderate respiratory distress. Apgar scores were 7 and 8 at 1 and 5 minutes, respectively. His weight was 3.3 kg (>90^{th} centile), length was 49 cm (80^{th} centile) and OFC was 36 cm (>> 90^{th} centile). He had (Figure 1 A, B) macrocephaly, hypertelorism, prominent eyes, pinpoint cataracts, low-set ears, overfolded helices, short neck, deep palmar creases, hyperextensible digits, tightly clenched fists with overlapping first and third fingers, spoon-shaped nails, extra folds of skin on the forearm, shoulder and back, hyperextensible elbows, large feet with overlapping toes, diffuse hypotonia and opisthotonic positioning.

Chromosome analysis was 46,XY. Costello syndrome was confirmed by molecular testing which revealed the typical missense mutation in the *HRAS* gene, p.Gly12Ser. Two-dimensional echocardiogram showed mild pulmonic valve stenosis, without cardiac hypertrophy. Nearly continuous atrial tachyarrhythmias (Figure 2 A, B) were interpreted at

various times as SVT, chaotic atrial rhythm, multifocal atrial tachycardia, ectopic atrial tachycardia with variable AV block, and later, atrial flutter depending on P wave morphology and rhythm regularity. The maximal rate of 375 bpm was resistant to digoxin, propranolol, amiodarone, and flecanide. At age 3 months, and after 2 weeks of sinus rhythm, hemodynamically significant atrial tachycardia returned, resisting cardioversion. A tracheostomy treated epiglottic and vocal cord areas of soft tissue obstruction. The patient died at age 4 months following an episode of severe tachycardia. Parents declined autopsy.

CASE 2

This female was born to a 33-year-old G1 mother and 31-year-old father. The pregnancy was complicated by well-controlled insulin-dependent gestational diabetes. Multiple marker screening suggested an increased risk for Down syndrome (1:237). Polyhydramnios noted at 24 weeks gestation became severe at 27 weeks necessitating amnioreduction (AFI 52 to 28 cm). Fetal MRI at 27 weeks showed ventricles at the upper limits of normal size. At 30 weeks, fetal edema and bilateral pleural effusions developed, and a second amnioreduction was performed. Fetal echocardiogram at 30 weeks gestation saw no structural anomalies or pericardial effusion, only PACs. Worsening fetal edema and bilateral pleural effusions led to scheduled Caesarean delivery at 32 weeks. Placental enlargement was present with a weight of 793 g (normal range 250–450 g). Birth weight was 2.7 kg (> 90th centile); estimated dry weight was 2 kg (75th centile). Length was 40 cm (25th centile). OFC 34.5 cm (>90th centile), but affected by severe edema. Apgar scores were 2 and 7 at 1 and 5 minutes, respectively. A protruding tongue (Figure 3), widely spaced nipples and hyperconvex nails were seen. Echocardiogram at age 2 days was normal. At age 11 and 18 days, there was sinus tachycardia (189–192 bpm) with multifocal PACs. Electrocardiogram tracings at 18 and 27 days showed a wide QRS tachycardia (198–203 bpm) consistent with ventricular tachycardia although atrial tachycardia with aberrant conduction could not be ruled out. Recurring pleural effusions and chylothorax necessitated chest tubes, and multi-organ failure ensued with death at age 40 days.

On autopsy, lung hypoplasia, nephromegaly and a liver hemangioma were noted. Multiple chromosome studies performed on amniocytes and peripheral blood cells had been normal, as was molecular testing for *PTPN11, SOS1, KRAS* and *RAF1* mutations. However, postmortem molecular testing detected an *HRAS* mutation resulting in a predicted p.Gly12Cys amino acid change, consistent with Costello syndrome.

CASE 3

This female, born to a 39-year-old G2 mother and unrelated 41-year-old father, developed SVT at 24 weeks gestation treated successfully with maternal digoxin and sotalol. Prenatal ultrasound showed polyhydramnios, hepatomegaly, thickened nuchal fold, macroglossia and shortened limbs. Labor was induced at 36 weeks gestation. The birth weight was 2.8 kg (50th centile), length 43 cm (5th centile) and OFC was 34 cm (75th centile). She had coarse facial features with a prominent forehead, periorbital fullness, epicanthal folds, small midface with an upturned nose, dysplastic and thickened ears, short neck with a wide chest, widely spaced nipples, and short thickened hands. At age 4 months, deep palmar creases and

excess skin over the dorsal aspects of her hands and feet were noted. Tracheostomy and gastrostomy tubes were required by age 3 months (Figure 4).

Serial echocardiograms showed biventricular hypertrophy, and mildly thickened atrioventricular valve leaflets. Refractory tachyarrhythmias showed variable P wave morphology described at various times as SVT, atrial fibrillation, atrial flutter, and occasional wide QRS tachycardia, though ultimately diagnosed as chaotic atrial rhythm. While reasonably well-controlled with digoxin, sotalol, and flecainide, she became markedly bradycardic, with sinus pauses up to 8 seconds, ultimately leading to pacemaker insertion at age 3 1/2 months. At age 9 months, she began having prolonged episodes of wide QRS tachycardia (greater than 40 minutes), for which sotalol and digoxin were discontinued and amiodarone was initiated. Systemic hypertension, with blood pressure ranging from 130–140/95, developed at age 10 months. While hospitalized at age 13 months, she had cardiovascular collapse with a terminal rhythm reported as ventricular tachycardia and fibrillation.

Postmortem examination of the heart confirmed the absence of structural heart defects, and normal semi-lunar and mitral valves, with slight redundancy of the tricuspid valve leaflets. There was hypertrophy of the left ventricle (left ventricle free wall 9 mm) and interventricular septum (15 mm), with mild subaortic stenosis. Microscopic examination showed mild disorganization of the myofibers, mainly in the central region. The coronary arteries and intra-myocardial vessels, pulmonary artery and aorta were normal. Neuropathological examination was consistent with old hypoxic-ischemic injuries. Storage disease, especially mucopolysaccharidosis, had been considered in the first months of life. Costello syndrome was suspected at age 3 months and confirmed by *HRAS* mutation testing two years postmortem showing the most common p.Gly12Ser mutation.

Literature Review and Natural History Study—Cases from the English literature from 1971 to 2008 were assigned to Group I (pre-*HRAS*) or Group II (*HRAS* confirmed). Group I cases required adequate clinical description and/or photograph. We excluded reviews with limited prenatal history (Lin *et al.*, 2002; Axelrad *et al.*, 2004; Gripp *et al.*, 2005; Aoki et al., 2005; Della Marca *et al.*, 2006; Axelrad *et al*., 2007; Schulz *et al*., 2008), and mosaicism (Gripp, *et al.* 2006; Sol-Church et al., 2009). We mailed a data collection form to the parents of *HRAS* mutation positive patients who had been enrolled in an ongoing natural history study of Costello Syndrome (Group III), and also included 3 additional cases cared for by authors.. Informed consent was obtained based on a protocol at the A. I. duPont Hospital for Children (IRB #2003-006 and #2005-051). Mutation analysis and clinical methods were performed as described previously (Gripp *et al*., 2006). Although chaotic atrial rhythm, chaotic atrial tachycardia and multifocal atrial tachycardia are equivalent terms (Walsh and Triedman, 2001; Walsh et al; 2006), but we used the former in this paper.

RESULTS

There were 222 Costello syndrome cases in Groups I (98), II (107) and III (17) (Table I). Groups II and III had molecular confirmation, but differ because of ascertainment. Though

the smallest, Group III provided the most information since all parents completed the questionnaire, and most of medical information was validated from medical records.

Polyhydramnios occurred in at least two-thirds (mean 79%) of cases in all groups, often reported as “severe”, “marked”, or requiring serial amniotic fluid reduction. Advanced paternal (> 35 years) and preterm delivery (< 37 gestational weeks) were reported approximately half of the cases. A detailed analysis of the causes of prematurity was not possible, but polyhydramnios occurred in 64% and 78% in Groups II and III, which did not differ from overall frequency. In Group III, at least one other abnormality was identified in addition to polyhydramnios in 9 of 17 (53%). Infrequent findings included hydrops (ascites, pleural and/or pericardial effusions), nuchal thickening, shortened long bones and abnormal hand posture.

Any type of cardiac abnormality was reported postnatally in 67%, 76% and 82%, with prenatal detection in 6%, 2%, 29% of cases in Groups I, II and III, respectively (Table 1). The absence of prenatal hypertrophic cardiomyopathy was striking since this was reported postnatally in 45%, 55% and 41% of cases in Groups I, II and III, respectively. A congenital heart defect was reported in one fetus from Group I (small ventricular septal defect in Siwik *et al.*, 1998), and postnatally in 19%, 17% and 47% of Group I, II and III, respectively (Table 2).

Arrhythmia occurred prenatally in 6%, 2%, and 29%, and postnatally in 24%, 35% and 82% in Groups I, II and III. Case 1 and Case 3 had prenatal SVT and later developed postnatal atrial tachycardia with multiple P wave morphology, interpreted as multifocal or chaotic atrial rhythm/tachycardia (Walsh *et al*., 2006). The frequency of a fetal arrhythmia in Costello syndrome can be estimated as 9/222 (4%) total cases, 7/222 (3%) excluding two cases with premature atrial contractions, or 4/222 (2%) excluding the 3 new cases.

DISCUSSION

The severe neonatal (Hinek *et al*., 2005; Digilio *et al*., 2007; Lo *et al.*, 2007) and prenatal characteristics of Costello syndrome have been described in case reports and table summaries listing polyhydramnios (Philip and Sigaudy, 1998; Zampino *et al*., 2006; Digilio *et al.*, 2007), increased nuchal thickness on early screening ultrasound (Kerr *et al.*, 1998) and large size for gestational age (Fryns *et al*., 1996; Van den Bosch *et al*., 2002). Moroni *et al.* (2000) provided the first prenatal images of one case noting that ultrasound examinations were normal until the third trimester when macrosomia and polyhydramnios developed. Although prenatal cardiac abnormalities were not reported, hypertrophic cardiomyopathy was observed at age five months. Costello syndrome has been associated with advanced paternal age (Lurie, 1994; Zampino *et al.*, 2007), reflecting the paternal origin of most, but not all, Costello syndrome causing mutations (Sol-Church *et al*, 2006).

We confirm the high frequency of polyhydramnios which can be severe. Three skeletal markers are nonspecific, observed with skeletal dysplasia or chromosome abnormality syndromes, i.e. shortened long bones, macrocephaly and abnormal hand posturing. Likewise, the detection of hydrops, ascites, pleural and/or pericardial effusions, large for

gestational age, nuchal thickening, and ventriculomegaly are not diagnostic for Costello syndrome. Polyhydramnios and other ultrasonographic markers were present in over half of the well-studied cases in Group III. In addition to polyhydramnios, the 3 new cases show some of the less common findings of the severe neonatal phenotype (Lo *et al.*, 2007), such as pleural effusions, need for tracheostomy and early death. In our study, there was no correlation between the presence of a fetal arrhythmia and polyhydramnios, hydrops, ascites or effusion (data calculated, but not shown on Table 1).

Fetal atrial tachycardia

This study highlights the importance of fetal arrhythmia in Costello syndrome, which is usually diagnosed *in utero* as SVT and followed postnatally by atrial tachycardia, especially chaotic atrial rhythm. In contrast to ectopic atrial tachycardia in which there is a single non-sinus atrial focus, chaotic atrial rhythm reflects multiple (≥ 3 P waves) foci of enhanced automaticity (Walsh *et al.*, 2006). Chaotic atrial rhythm is usually idiopathic in children, or may occur postoperatively with a congenital heart defect. The occurrence with Costello syndrome has been reported (Lin *et al*., 2002; Gripp *et al*., 2006), and appears to be the most common syndromic association. Thus, chaotic atrial rhythm in an infant with polyhydramnios, high birth weight, edema, unusual facial features, and joint laxity, especially when accompanied by hypertrophic cardiomyopathy, and/or pulmonic stenosis, should lead to an evaluation for Costello syndrome.

Among literature and new patients with a nonspecific fetal SVT followed by postnatal chaotic atrial rhythm (Table 2), none have had ECG tracings to document its prenatal characteristics. Costello syndrome should be considered when polyhydramnios, ascites, thick nuchal fold, large for gestational, and shortened femurs are accompanied by SVT. The postnatal electrocardiogram tracings (Figure 2) of Case 1 show representative examples of chaotic atrial rhythm, which may pose a diagnostic and management challenge to the pediatric cardiologist.

Fetal intermittent extrasystoles are usually hemodynamically insignificant, except when they initiate sustained tachycardia. Two patients (Case 12, new patient 2) had only fetal PACs and later developed serious postnatal tachycardia including chaotic atrial rhythm (Case 12) and wide QRS tachycardia (new patient 2) suggesting that their appearance in a fetus with suspected Costello syndrome may have prognostic value. Symptomatic fetal tachycardias are usually supraventricular in origin and may be associated with the development of hydrops fetalis (Kleinman and Nehgme, 2004). In our study, there was no correlation between the presence of an arrhythmia and polyhydramnios, hydrops, ascites, pleural or pericardial effusions. Patients with fetal arrhythmias may respond to anti-arrhythmic drugs, given either through the maternal or fetal route. There is insufficient data to generalize the predictive value of response to maternal therapy in Costello syndrome fetuses. The persistence of fetal atrial tachycardia in Case 1 was consistent with failure to respond to antiarrhythmic therapy postnatally.

Comparison with other Ras/MAPK syndromes

Currently, chaotic atrial rhythm appears to distinguish Costello syndrome from other syndromes in the Ras/MAPK pathway (Lin *et al.*, 2002; Gripp *et al.*, 2007). The Cardiofaciocutaneous (CFC) syndrome is also associated with a similar frequency of polyhydramnios and prematurity in a smaller series (Armour and Allanson, 2008). Prenatal ultrasonographic findings have been reported in two patients with CFCS and polyhydramnios, increased nuchal translucency, pyelectasis, ventriculomegaly, macrosomia and short femurs, similar to the features in the Costello syndrome patients in this report (Witters *et al.*, 2008). Fetal atrial tachycardia was not observed.

Study limitations and strengths

In this descriptive study, statistical analysis of genotype-phenotype correlation was not possible because it is skewed in favor of the *G12S* mutation. The prenatal information for Group II was not collected in a systematic fashion, and there is a bias of ascertainment in Group III because the 3 cases were chosen for their antenatal cardiac presentations.

An important question for the future is whether these common or distinctive feature will enhance the diagnosis of Costello syndrome. The lack of prenatally diagnosed hypertrophic cardiomyopathy in the ~50% who develop it later in life raises interesting questions about the pathophysiology of this cardiac “overgrowth”. The absence of fetal hypertrophic cardiomyopathy may be due to a lack of sensitivity of prenatal echocardiographic detection of mild forms, or may reflect the natural history of hypertrophic cardiomyopathy which appears to increase in severity as the period of failure to thrive progresses. Similarly, the lack of prenatal pulmonic stenosis may reflect the prevalence of mild forms or natural history of the defect. Future analysis could study the timing of the ultrasound markers, and whether they are second trimester findings which would permit the diagnosis at a time to change the pregnancy management.

CONCLUSION

The fetal phenotype of Costello syndrome consists of polyhydramnios, macrocephaly, large size for gestational age, shortened long bones and ventriculomegaly, which may be nonspecific ultrasonographic findings when observed alone, but together lead to a suspicion for Costello syndrome. This suspicion would be substantially strengthened by the occurrence of a fetal atrial tachycardia. Since amniocentesis will likely be offered to exclude more common causes of polyhydramnios and short limbs, concomitant *HRAS* testing in affected fetuses could be considered. Costello syndrome results in mental retardation, increased malignant tumor risk and multiple anomalies, and timely prenatal diagnosis will provide important options for pregnancy management. Pregnancy outcomes could be improved by increasing the awareness for (1) potential arrhythmias, (2) preterm labor, and (3) large for gestational age fetuses or macrocephaly which may alter delivery management.

ACKNOWLEDGEMENTS

Katia Sol-Church is supported by funds from the NCRR to the Biomolecular Core Laboratory (NIH P20-RR020173) and by the Nemours Foundation.

We extend our gratitude to many colleagues for their expertise in diagnosing and caring for these children, and assistance in research for this paper including Drs. Patricia Dickson, Elizabeth Goldmuntz, Prapti Kanani, Elizabeth Roeder, Steven Seidner, and Robert Stratton, and Ms. Elizabeth Hopkins and Meghan Muir. We are indebted to the parent leaders (Dawn Macready Santos, Lisa Schoyer, Colin Stone), the parents and individuals of the International Costello Syndrome Family Network.

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ADDENDUM

At the time of submission, we became aware of a publication which reported the first prenatal amniocentesis diagnosis of Costello syndrome (Kuniba J, Pooh RK, Sasaki K, Shimokawa O, Harada N, Kondoh T, Egashira M, Moriuchi H, Yoshiura K, Niikawa N. 2008. Prenatal diagnosis of Costello syndrome using 3D ultrasonography amniocentesis confirmation of the rare *HRAS* mutation G12D. Am J Med Genet Part A. DOI 10.1002/ajmg.a.32335). Prenatally, this 31 week old male had polyhydramnios, increased fetal weight and head circumference, suggestive facial appearance, wrist deviation. There was no advanced paternal age, prenatal effusions, ascites, edema, brain anomalies, macroglossia, short limbs, or cardiac problems. The uncommon G12D mutation was detected. “Cardiac hypertrophy” was noted, but not further characterized.

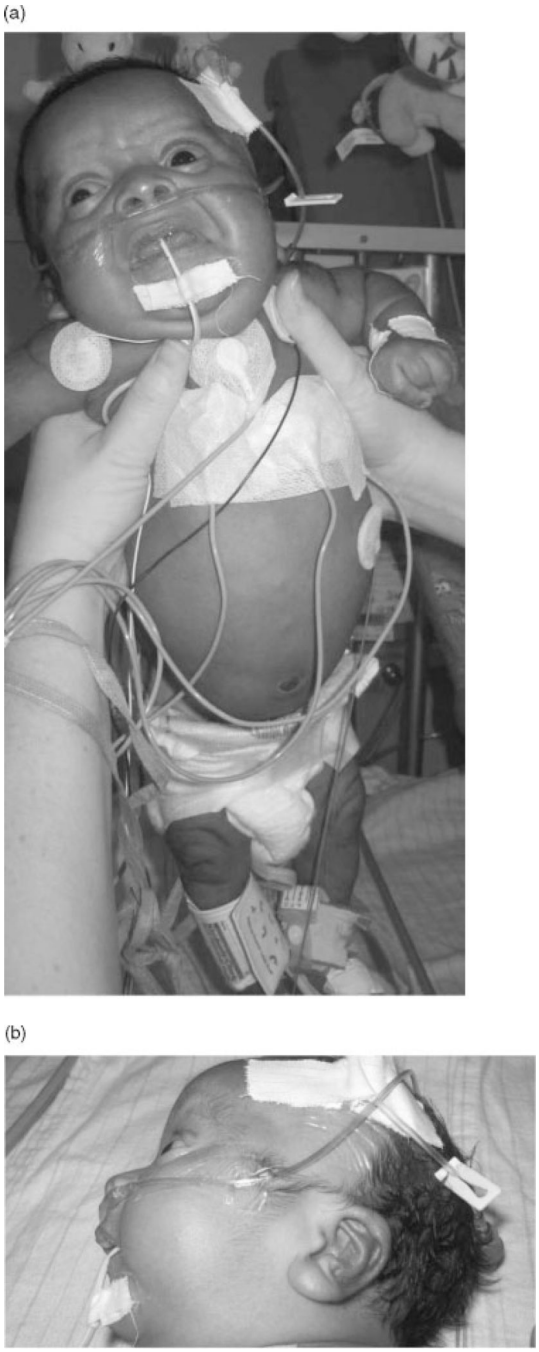

Figure 1.

Case 1. Typical features of a newborn with Costello syndrome showing (A) hypertelorism, wrinkled skin, short nose, full nasal tip, wide mouth, full, prominent lips and clenched hand with overlapping fingers (reminiscent of, but distinct from, trisomy 18 syndrome); (B) and in lateral view the low-set ears with fleshy lobule.

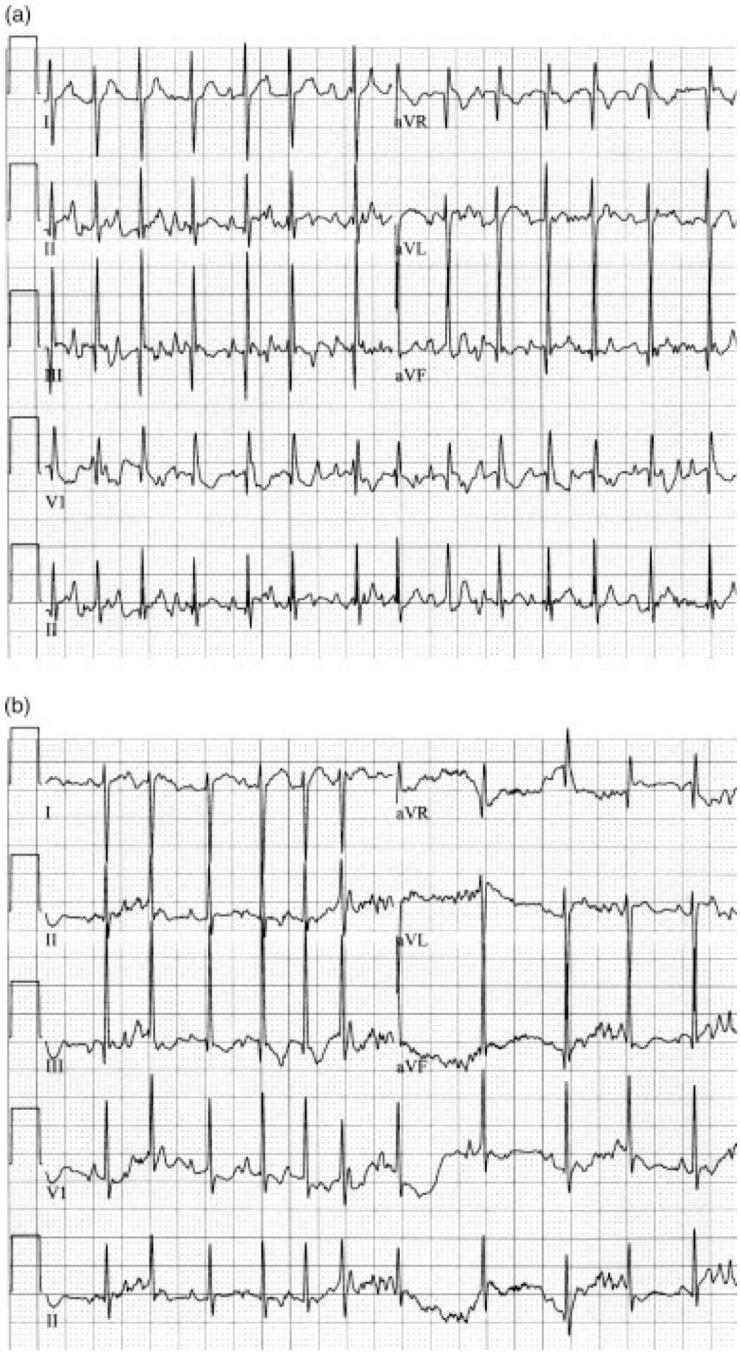

Figure 2.

Case 1. Postnatal electrocardiograms illustrate chaotic atrial rhythm. (A) Day of life 3: Bouts of CAR start and stop, with evidence of multiple P wave morphologies and faster AV conduction (mean HR 200). (B) At 7 weeks of age, the tachycardia appears less chaotic, but multiple P waves are again noted.

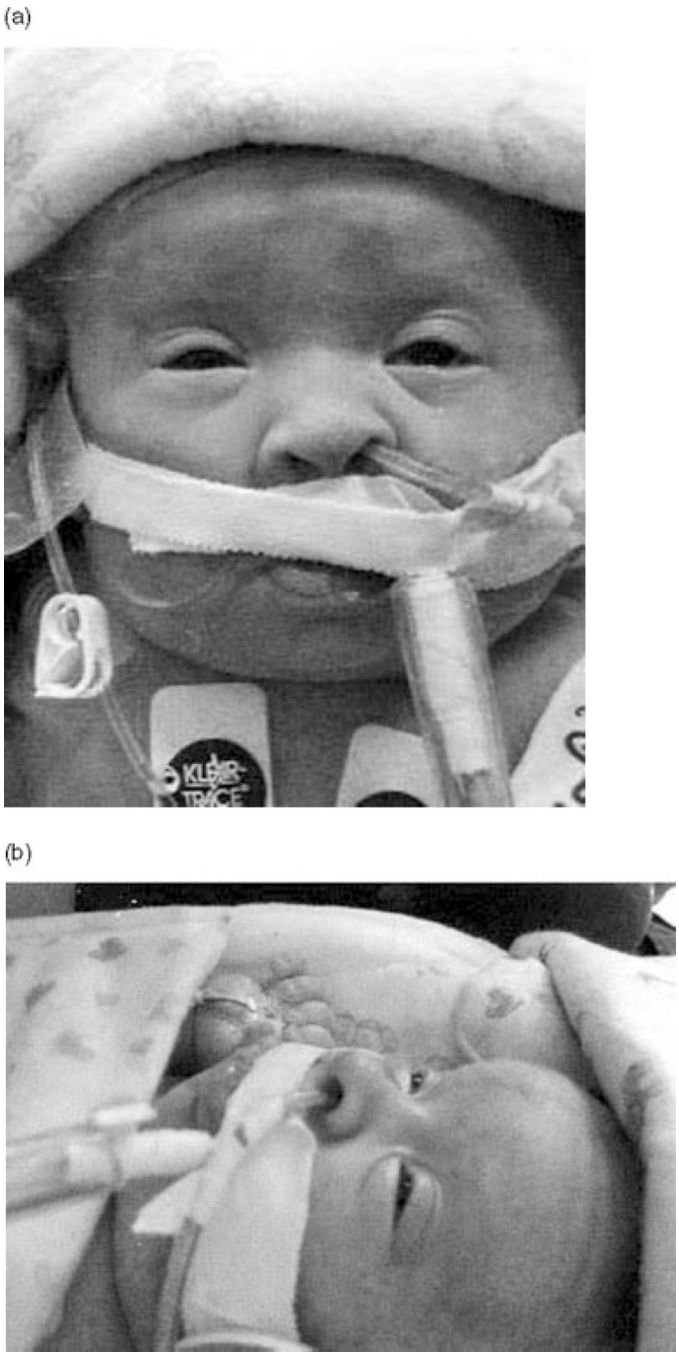

Figure 3.
Case 2, frontal and lateral. The facial features of Costello syndrome are illustrated in this premature infant, though obscured by the endotracheal and feeding tubes, and adhesive tape. There is a full nasal tip, periorbital puffiness and protruding tongue.

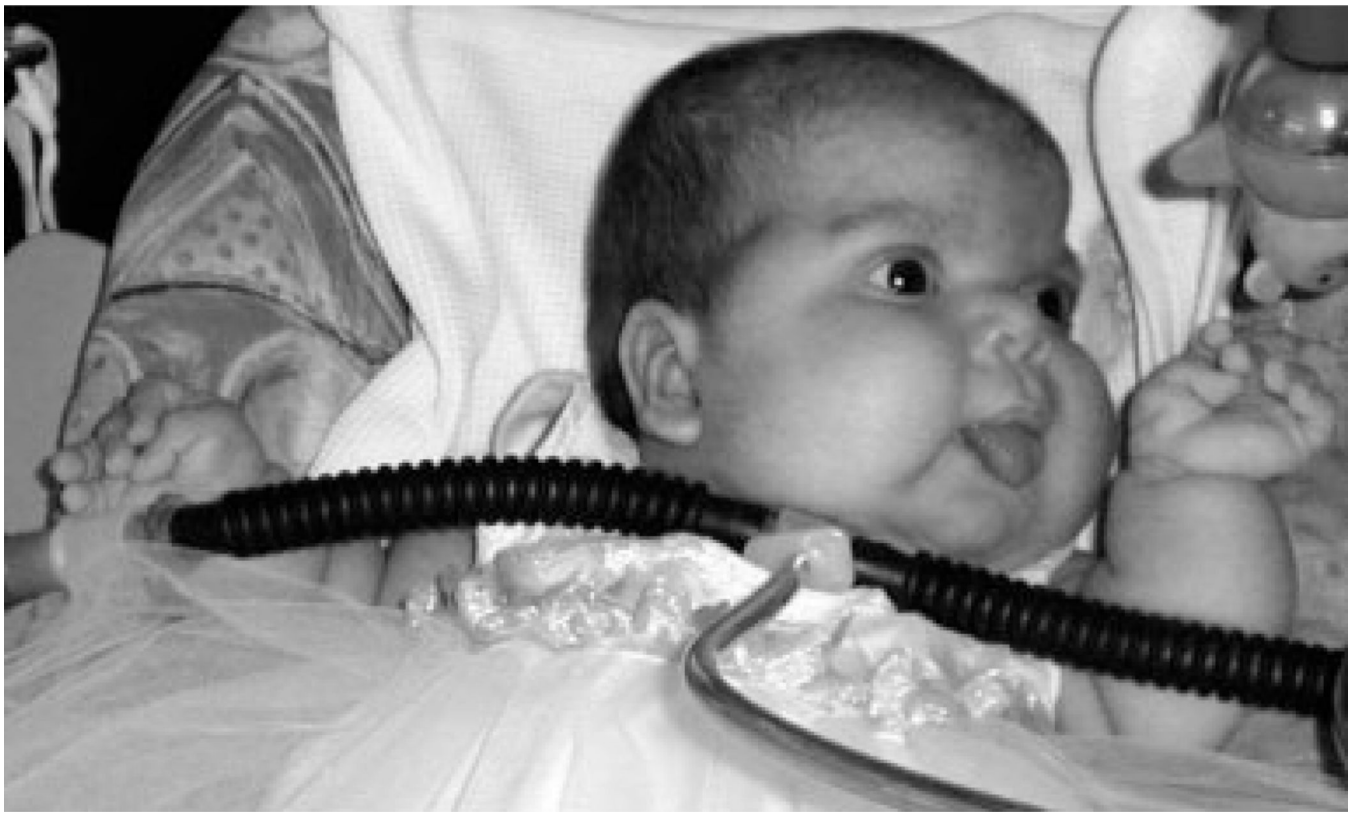

Figure 4.

Case 3. This child also has the distinctive clenched hands with overlapping fingers, short nose, full nasal tip, thick earlobe and periorbital fullness.

Table 1

Prenatal features of patients with Costello syndrome: 98 literature cases identified before the period of *HRAS* gene diagnosis (Group I), 107 literature cases with *HRAS* confirmation (Group II), and 17 new cases (14 from natural history study, 3 contributed cases) (Group III).

Feature	Group I[1] n=98	Group II[2,3] n= 107	Group III n=17
	Denominator reflects number of informative cases		
Male	52/97 (54%)	30/66(45%)	9/17 (53%)
Female	45/97 (46%)	36/66 (54%)	8/17 (47%)
Advanced maternal age (>35 years)	10/66 (15%)	5/12 (42%)	3/16 (19%)
	Mean 30.5	Mean 33.1	Mean 31.6
Advanced paternal age (>35 years)	29/68 (43%)	13/21 (62%)	7/16 (43%)
	Mean 34.4	Mean 37.2	Mean 37.1
Preterm delivery (<37 weeks)	34/85 (40%)	11/22 (50%)	9/17 (53%)
Ultrasound findings;			
Polyhydramnios[4]	48/71 (68%)	55/60 (92%)	13/17 (76%)
Severe	2/48 (4%)	6/55 (11%)	3/13 (23%)
Nuchal thickening	1/48 (2%)	3/55 (5%)	2/17 (12%)
Ascites, effusions, and/or hydrops	0	3/55 (5%)	2/17 (12%)
Shortened long bones	0	2/55 (4%)	5/17 (29%)
Abnormal hand posturing	0	2/55 (4%)	0
Ventriculomegaly	0	0	3/17 (18%)
Macrocephaly	12/48 (25%)	9/18(50%)	3/17 (18%)
Prenatal cardiac abnormalities	4/71 (6%)	1/58 (2%)	5/17 (29%)
	1 Arrhythmia nos	1 Tachycardia nos	3 SVT
	1 VSD nos		2 PACs
	1 Tachycardia nos		
	1 PAT		

[1] Costello *et al*., 1977 and Costello *et al*., 1996; Der Kaloustian *et al*., 1991; Martin and Jones, 1991; Borochowitz *et al*., 1992; Teebi *et al*., 1993; DiRocco *et al*., 1993; Izumikawa *et al*.,1993; Kondo *et al*.,1993; Patton *et al*., 1993; Phillip and Mancini, 1993; Zampino *et al*., 1993; Say *et al*., 1993; Yoshida *et al*., 1993; Davies *et al*., 1994; Okamoto *et al*., 1994; Fryns *et al*., 1994; Torres *et al*., 1994; Umans *et al*., 1994; Torrelo *et al.*, 1995; Mori *et al*., 1996; Fukao *et al*., 1996; Johnson *et al*., 1998; Pratesi *et al*., 1998; Tomita *et al.*, 1998; Siwik *et al*., 1998; Franceshini *et al.*, 1999; Szalai *et al*, 1999; van Eeghen *et al*., 1999; Bisogno *et al*., 1999; Innes and Chudley, 2000; Moroni *et al*., 2000; Sigaudy *et al*., 2000; Hatamochi *et al*., 2000; Boente *et al.*, 2001; Gripp *et al.*, 2002; Kaji *et al*., 2002; Kamoda *et al*., 2002; van den Bosch *et al*., 2002; Urakami *et al*., 2002; Kawame *et al.*, 2003; Delrue *et al.*, 2003; Mancini *et al*., 2003; DiRocco *et al*., 2003; Nasca *et al.*, 2003; Cakir *et al*., 2004; Waldburg *et al*., 2004; Dickson et al., 2004; Gregersen *et al*., 2004; Stein *et al.*, 04; Hinek *et al.*, 2005; Alexander *et al*., 2005; White *et al*., 2005.

[2] Lin *et al*., 2008 represented the compilation of Gripp *et al*., 2006 and Estep *et al.*, 2006; Kerr *et al*., 2006; Steens *et al.*, 2006; Zampino *et al.*, 2006; Digilio *et al*., 2007; Limongelli *et al*., 2007; Denayer *et al*., 2007; Lo *et al*., 2008; Hou *et al*., 2008; Gripp *et al.*, 2008.

[3] Case reports in the literature who were later included in extensive reviews were generally reported only in Group II, e.g. patients 1 and 3 in Zampino *et al.*, 1993 were also patients CS-01 and CS-04 in Zampino *et al.*, 2006).

[4] Polyhydramnios was recorded if reported by ultrasonographic examination, and in one additional patient observed clinically at delivery.

CAR, chaotic atrial rhythm; NOS, not otherwise specified; NS, not stated; PACs, premature atrial contractions; PAT, paroxysmal atrial tachycardia; VSD. Ventricular septal defect; SVT, supraventricular tachycardia

Table 2

Prenatal and subsequent postnatal features of cardiac abnormalities in Costello syndrome.

Group I n=98	Group II n= 107	Group III n=17	Outcome of respective patients
Prenatal findings			**Subsequent postnatal**
Siwik et al., 1998 35 weeks, male VSD, small (nos)			VSD, perimem Severe HCM, BVH Frequent PACs
Gripp et al., 2002 Case 2 33 weeks, female Tachycardia			EAT
Gripp et al., 2002 Case 3 37 weeks, female PAT			SubPS HCM Atrial fibrillation
Dickson, et al., 2004 35 weeks, male Arrhythmia (nos)			Coarctation Abnormal aortic valve HCM "Multiple SVTs", CAR[1]
	Lin et al., 2008 Case 42 (Estep et al., 2006) Tachycardia nos		HCM
(Previously reported in Berberich et al., 1990; Johnson et al, 1998 Case 4)		Natural history study case 11 Term, male SVT	PS, BAV HCM SVT
(Previously reported in Gripp et al., 2006; Lin et al., 2008)		Natural history study case 12 34 weeks male PACs	EAT, PAT, MAT, SVT, CAR
		New case 1 36 weeks male SVT, PACs	PSV SVT, EAT, MAT, CAR
		New case 2 32 weeks, female PACs	Sinus tachycardia with PACs and VT (or atrial tachy with aberrant conduction)
		New case 3 36 weeks, female SVT	SVT, wandering atrial pacemaker, CAT,

[1]The postnatal arrhythmias were re-evaluated by the authors of the original paper and A.E.L. and C.B. who reviewed the original electrocardiograph tracings (Dickson *et al.,* 2001, personal correspondence). Chaotic atrial rhythm was present.

BAV, bicuspid aortic valve; BVH, biventricular hypertrophy; CAR, chaotic atrial rhythm; CAT, chaotic atrial tachycardia; EAT, ectopic atrial tachycardia; HCM, hypertrophic cardiomyopathy; NOS, not otherwise specified; NS, not stated; PACs, premature atrial contractions; PAT, paroxysmal atrial tachycardia; PS, pulmonic stenosis; SVT, supraventricular tachycardia; VSD, perimem, Ventricular septal defect, perimembranous; VT, ventricular tachycardia