Short reports

Costello syndrome in two Brazilian children

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Abstract

The increasing number of children with Costello syndrome described world wide has helped in delineating further the characteristic features of this condition. We report here two children, seen in the Genetic Division of the Brasilia University Hospital, showing the main features of the syndrome: "coarse" face, redundant skin on the feet and hands, hyperextensible hand and finger joints, curly hair, growth and psychomotor retardation, and feeding problems. In addition, one of the patients developed hydrocephalus during the evolution of the disease, making the third published patient with this complication. We discuss the appropriateness of serial brain imaging studies in Costello syndrome in light of the relative frequency of central nervous system malformations.

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The syndrome originally described by Costello in 1971¹ and further delineated by the same author in 1977² is characterised by poor postnatal growth, mental retardation, curly hair, coarse face, and nasal papillomata. Following a lapse of several years after the initial publication two new patients were reported in 1991 by Der Kaloustian *et al*³ and Martin and Lyons Jones.⁴ Since then several additional patients have been described.⁵⁻²¹

We describe two new children with Costello syndrome emphasising the presence of obstructive hydrocephalus in one of the patients, as previously reported in a 27 month old child described by Say *et al*⁷ and in an adult patient by Zampino *et al*.¹⁰

Case reports

PATIENT 1

Patient 1, a boy, is the second child of a healthy, non-consanguineous 33 year old mother and 42 year old father. The patient has an older, healthy sister. The pregnancy was uneventful, except for the presence of polyhydramnios seen on abdominal echography performed during the seventh month of gestation. The child was born at 37 weeks of gestation by caesarian section with Apgar scores of 3 at one minute and 8 at five minutes. The birth weight was 3840 g

(75th centile), length 51 cm (50th centile), and occipitofrontal circumference (OFC) 37.5 cm (>90th centile). The infant developed transient respiratory distress owing to aspiration and fed poorly because of difficulties in swallowing. After having developed aspiration pneumonia at 2 months of age the patient was fed through a nasogastric tube until he was 4 months of age. Some degree of difficulty in swallowing was still present at the end of his second year. During his first three days of life he had two seizures and was started on phenobarbital. He also displayed a systolic murmur grade III/IV and had frequent episodes of severe cardiac tachyarrhythmia, which were successfully treated with digoxin and anti-arrhythmic medication which was maintained until his second year of life.

Clinical examination at the age of 4 months disclosed an infant with poor body growth and delayed motor development. Weight was 4400 g (<3rd centile), length was 59 cm (<3rd centile), and OFC was 41 cm (25th centile). The hands and feet showed deep palmar and plantar creases and markedly loose skin, especially on the neck and extremities. Bilateral inguinal hernias and a left undescended testis were also observed. He had a normal (46,XY) karyotype. A Doppler echocardiographic study performed at 1 year of age was indicative of a moderate degree of valvular and supra-ventricular pulmonary stenosis. A CT scan of the head, performed at 1½ years of age showed large lateral ventricles and third ventricle and obstructive hydrocephalus that was surgically corrected through a ventriculoperitoneal shunt.

Another evaluation at the age of 7 years 10 months showed a mentally retarded child with a sociable and pleasant personality. He was capable of expressing himself through single words and his voice was deep and hoarse. He had a marked delay in growth, despite showing a comparatively large, dolichocephalic head. His weight was 17.2 kg (<3rd centile), his height was 102 cm (<3rd centile), and the OFC was 53 cm (>50th centile). He was very ticklish, making physical examination quite difficult. He had coarse facial features and increased skin pigmentation compared to his family. His hair was light, sparse, and curly. He had a prominent forehead with low frontal hairline, palpebral fissures with a downward slant, and an epicanthic fold on the left. He also displayed convergent strabismus, midfacial hypoplasia, retrognathia, ocular hypertelorism,

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Figure 1 (A, B) Patient 1 at 1 year of age showing sparse hair, relative macrocephaly, and elbow and knee limitation. (C, D) The same patient aged 8 years showing low set ears with thick lobes, sparse, curly hair, and a "coarse" face. (All photographs reproduced with permission.)

and a wide based nose with a depressed nasal root, rounded tip, and anteverted nostrils. His nasal bridge was depressed. Several warty papules were present on the malar region, principally around the nose. His mouth was wide and carp shaped with prominent, full lips and a high arched palate. Dental malocclusions and dysplastic, low set, and posteriorly angulated ears with thick, prominent lobes were also present. His neck was short with redundant skin (fig 1). His hands showed redundant skin on the dorsum and mild hyperkeratosis of the palms. Large calluses were seen on friction areas of both hands and feet. Hyperextensibility of the fingers and wrist joints, ulnar deviation of the hands, and cutaneous syndactyly of the proximal phalanges of all fingers were noted bilaterally. The nails were thin and deep set. Talipes equinovarus was present on both sides, more severe on the left. There was also pectus carinatum and thoracic kyphoscoliosis. Skeletal radiographs disclosed a bone age of 4 years and bilateral hip subluxations. His shoulders were in a permanent downward position. A small midline depression was seen in the sacral region. Tightness of the Achilles tendon, limitation of extension of the elbows and knees, and malposition of the toes with a proximally seated second toe overriding the other toes were observed bilaterally. He also showed a moderate plantar hyperkeratosis and dystrophic toenails. His penis was 3 cm long (<10th centile).

PATIENT 2

Patient 2, a girl, is the third child of healthy, unrelated parents. At the time of birth, her father and mother were both 30 years old. The patient's two older brothers are normal. The child was born by caesarian section following

Figure 2 Clinical appearance of patient 2 at 7 months of age; note (B) redundant skin on neck and extremities.

an uneventful pregnancy. Her birth weight was 4220 g (95th centile), length 48 cm (<10th centile), and OFC 35 cm (>50th centile). Abnormal facial features as well as lax skin were noted at birth. She was dolichocephalic with prominent scalp veins. Umbilical hernia was also noted. The neonatal period was complicated by respiratory distress, feeding difficulties, and transient hypoglycaemia. She had a grade II/IV systolic murmur and a Doppler echocardiogram disclosed the presence of interatrial septal communication, probably ostium secundum. Peripheral blood G banded chromosomes showed a normal female karyotype (46,XX). A presumptive diagnosis of leprechaunism was made at that time.

The child was re-evaluated at the age of 7 months because of failure to thrive, dysmorphic features, and developmental delay. Her weight was 3990 g (<3rd centile), her length was 55 cm (<3rd centile), and her OFC was 38 cm (<3rd centile). Her bone age was 3 months. She displayed a "coarse" face (fig 2A), with short and sparse hair, epicanthic folds, depressed nasal bridge, low set ears, moderately large mouth and macroglossia, high arched palate, short neck, redundant skin on the neck and extremities (fig 2B), deep palmar and plantar creases, limited extension of the elbows, and hyperextensible finger joints. Moderate generalised hypertonia with a tendency to opisthotonus was also observed. Results of blood and urinary examinations, including T3, T4, and TSH, were normal, except for an abnormally low level of IgA. A new Doppler echocardiogram at 8 months of age disclosed, in addition to the previous findings, severe pulmonary stenosis and a hypertrophic right ventricle. Cranial CT scan showed mild cerebral atrophy. After discharge

Table 1 Clinical findings in Costello syndrome

	Reported cases ^{1 3-18 20 21}	Patient 1	Patient 2
General findings			
Polyhydramnios	12/21	+	-
Large for gestational age	12/18	+	+
Poor feeding	20/20	+	+
Postnatal growth retardation	21/21	+	+
Central nervous system anomalies			
Cerebral atrophy	7/12	-	+
Hydrocephalus	1/21	+	-
Psychomotor delay	21/21	+	+
Sociable personality	14/17	+	-
Craniofacial anomalies			
"Coarse" face	16/17	+	+
Absolute or relative macrocephaly	21/21	+	+
Downward slanting palpebral fissures	12/15	+	+
Epicanthic folds	14/16	+	+
Strabismus	7/15	+	-
Depressed nasal bridge	14/17	+	+
Thick lips	18/21	+	+
Macroglossia	6/13	+	+
Large mouth	19/21	+	+
Low set ears with thick lobes	18/18	+	+
Musculoskeletal anomalies			
Short neck	16/17	+	+
Increased AP diameter of chest	13/15		
Herniae	5/11	+	+
Elbow limitation	13/16	+	+
Hyperextensible fingers	18/19	+	+
Wide distal phalanges	11/12	+	+
Ulnar deviation of hands	3/13	+	+
Tight Achilles tendon	13/16	+	-
Foot positional defects	8/12	+	-
Skin and adnexa anomalies			
Curly hair	16/16	+	-
Thin dystrophic nails	11/16	+	-
Loose skin on hands and feet	19/20	+	+
Deep plantar, palmar creases	19/19	+	+
Hyperkeratotic palms and soles	8/14	+	-
Dark skin pigmentation	16/21	+	-
Papillomata	12/18	+	-
Cardiac anomalies			
Hypertrophic cardiomyopathy	9/13	+	+
Dysrhythmia	7/13	+	+

from hospital the child's family moved to another city, precluding further follow up.

Discussion

After the original description and a lapse of almost 20 years, several new reports have helped to delineate Costello syndrome further.⁵⁻²¹ The two children reported here displayed all the main characteristics of the syndrome and are, as far as we know, the first two patients with Costello syndrome reported in South America. A comparison between the clinical findings in our patients and previously reported patients is shown in table 1.

As pointed out by Zampino *et al.*¹⁰ the natural history of Costello syndrome is characterised by two distinct phases. The first phase, up to the second or third year of life, is generally quite difficult. Pregnancy is frequently complicated by polyhydramnios and fetal overgrowth. After birth, significant growth retardation takes place and the patient's phenotype resembles that of protein calorie malnutrition. Nearly all patients fed poorly owing to swallowing difficulties. However, feeding difficulties are not the factor causing growth retardation and severe reduction of subcutaneous fatty tissue and muscle mass, since gavage or parenteral nutrition are ineffective in reversing the clinical picture. A significant delay in psychomotor development becomes progressively apparent during the first year followed by a relative catch up. Cardiac anomalies, mainly hypertrophic cardiomyopathy and paroxysmal atrial tachy-

cardia, are common. In our two patients supraventricular arrhythmias were quite distressing, being one of the main reasons for concern. Interestingly, both the cardiac problems and feeding difficulties tend to be spontaneously controlled during the second year of life. A relative macrocephaly is often observed, the head appearing larger in comparison to reduced body weight and height. This macrocephaly is frequently absolute, the OFC being above the 50th centile. The hair is thin and sparse and the skin is redundant and loose, especially on the neck and extremities. There is hyperextensibility of the joints, principally the fingers and wrists. The mouth is wide with thick lips and the ears are protuberant with thick lobes. In spite of so many signs and symptoms, the initial diagnosis can be difficult, and confusion may arise mainly with leprechaunism. Other syndromes that need to be considered in the differential diagnosis are Noonan and cardiofaciocutaneous syndromes. It is important, as pointed out by Fryns *et al.*²⁰ to consider the diagnosis of Costello syndrome in infants presenting the triad of polyhydramnios, fetal overgrowth, and postnatal failure to thrive. Other important and frequent features of this syndrome are poor feeding associated with swallowing difficulties and cardiac conduction anomalies. These findings are important for an early diagnosis because the typical dysmorphic features of the syndrome become conspicuous only between the ages of 1 and 2 years.

During the second phase of the disease, physical traits are more characteristic. Facial traits become "coarser", frequently arousing the suspicion of storage diseases. Papillomata in the perioral, nasal, and anal regions may appear at different ages, but generally after the second year. The hair is sparse and curly and the skin generally darker than that of parents and sibs. The swallowing difficulties subside and, with normal ingestion restored, a disproportionate weight gain relative to linear growth becomes apparent, but, in spite of this, both height and weight still remain below the 50th centile. The patients, despite their variable degree of mental retardation, are not disruptive being quite sociable and of a good natured disposition.

In Costello syndrome, neurological findings are variable and non-specific, being of little value in establishing the diagnosis. A generally mild cerebral atrophy and several other minor brain abnormalities have been seen on CT scan or MRI. Electroencephalograms generally only show non-specific alterations. Seizures are rarely observed in these patients. Hydrocephalus is an infrequent finding, having been reported only twice previously. Say *et al.*⁷ reported a patient with infantile spasms in whom hydrocephalus was detected at the age of 6 months. Zampino *et al.*¹⁰ also reported a patient who, at the age of 23, went into a coma as a result of hydrocephalus. In spite of being an apparently rare event hydrocephalus must be considered a possible complication of Costello syndrome, reinforcing the need for brain imaging studies in these patients.

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