Syndrome of the month

Costello syndrome

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Abstract
Costello syndrome is characterised by postnatal growth deficiency, coarse facies, redundant skin on the neck, palms, soles, and fingers, dark skin, acanthosis nigricans, and papillomata. The natural history evolves in two phases, a severe failure to thrive during the first months contrasting with a normal weight gain in later life. Cardiomyopathy is frequent but other visceral involvement is rare. Mild to moderate mental retardation is usual and most patients exhibit a characteristic sociable and friendly personality. The pathogenesis and molecular basis of the syndrome are unknown and the diagnosis is reliant on clinical expertise. Papillomata represent the most characteristic manifestation but may arise late in life. The peculiar course of the disease, the typical facies, and the ectodermal involvement with loose and hyperpigmented skin are characteristic enough to allow an early diagnosis. Most cases have been sporadic, suggesting de novo dominant mutations.

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In 1971, Costello1 2 described a new syndrome consisting of postnatal growth deficiency, mental retardation, coarse facies, and nasal papillomata. No further cases were reported until 1991 when Der Kaloustian et al3 and Martin and Jones4 reported children with the same manifestations. Since then, other cases have been reported.5–16 The pattern of anomalies is characteristic and the diagnosis is usually easy, even when the pathognomonic papillomata are not present.

Natural history
Polyhydramnios is noted in approximately one third of the pregnancies. Birth weight and length are usually normal or at the upper limit, contrasting with the final height. The course of the disease is marked by two successive phases. The first one, so-called marasmic, is characterised by severe postnatal failure to thrive. It remains unclear whether swallowing difficulties and poor sucking ability are responsible for the poor growth, since high calorie intake and tube feeding do not seem to improve weight gain in the first months of life. In later childhood, the linear growth deficiency persists but weight gain improves slowly. In two cases with a long term follow up, the final height was very short.17

Dysmorphic features
Relative macrocephaly is usual. The face is coarse, with downward slanting palpebral fissures, epicanthic folds, low nasal bridge, and a large mouth with thick lips (fig 1). The forehead is sometimes hairy. The neck is short and the ears are low set with typically large, fleshy, and prominent lobes. The thorax is large with an increased anteroposterior diameter. The hands and feet appear large with marked creases over the palms and soles (figs 2 and 3). The small joints, particularly those of the fingers, are hyperextensible, whereas limitation of larger ones, such as the elbow, has been reported in several cases. Positional foot defects are frequent and have been related to a tightness of the Achilles tendon (fig 4).

Cardiac involvement is frequent and a cardiac murmur is present in most cases. Ventricular septal defect, atrial septal defect, and pulmonary stenosis have been reported occasionally. Hypertrophic cardiomyopathy was documented in several instances and appears to be an important diagnostic and prognostic element. A systematic screening for cardiac anomalies is recommended. Other visceral involvement is rare. Umbilical hernias can occur. Benign tumours, such as epithelioma,4 or malignant ones, such as ganglioneuroblastoma,5 have been reported in some cases.
Costello syndrome

are large with redundant skin and nails is nigricans. Patchy hyperkeratosis is present. The hair is curly and the nails are small and deep set. The presence of papillomata is highly characteristic and this cutaneous manifestation has been considered mandatory for the diagnosis since Costello's first description. However, the age of onset of the papillomata is variable, between 2 years of age and late adolescence. This is probably the reason why the syndrome has been underdiagnosed for many years. These cutaneous growths resemble warts and are preferentially located in the perioral, nasal, and anal regions, but papillomata can be found on the trunk, limbs, and larynx. Histological findings are indistinguishable from those seen in verruca vulgaris.

CNS involvement

The occipitofrontal circumference is large at birth and relative macrocephaly is present in older patients. Hydrocephalus requiring ventriculoperitoneal shunt has been reported twice. Mild to moderate mental retardation is always present. The majority of patients are said to have a happy, outgoing personality. This behaviour seems consistent enough to be proposed as a diagnostic criterion.

Genetics

Most cases have been sporadic. Case reports have documented recurrence among sibs in one family and consanguinity in two others. This has led some authors to propose a recessive mode of inheritance. However, the consanguineous children were of Arabic-Druze ancestry in which consanguineous matings are frequent. Lurie carried out a segregation analysis from the 28 published cases. The results were consistent with a sporadic autosomal dominant mutation. A significant increase in the mean paternal age was also found and reinforced this hypothesis. Recurrences among sibs could be the result of germline mosaicism or genetic heterogeneity with a small proportion of recessively inherited cases. A single case presented with a balanced (1;22) translocation, suggesting that the two chromosomal breakpoints represent good candidate loci for the disease gene.

Differential diagnosis

It is now thought that the facio-cutaneous-skeletal syndrome described by Borochowitz et al. represents the same condition as Costello syndrome rather than a separate entity. There is some degree of overlap between Costello and Noonan and cardiofaciocutaneous syndromes since short stature, developmental delay, macrocephaly, curly hair, low set ears, and cardiac involvement are common to all three of them. Some cases of Costello syndrome are likely to have been misdiagnosed as having one of these conditions in the past. However, the particular redundancy of the skin over the hands and feet, the deep palmar and plantar creases, the olive skin colouration, the papillomata, the foot position defects, and subtle dysmorphic features, such as thick and prominent ear lobes and a large mouth with thick lips, are characteristic enough of Costello syndrome to differentiate it from these clinically related conditions. In infancy, Costello syndrome can be mistaken
for leprechaunism and two cases had been diagnosed as having “congenital cutis laxa with retarded growth and development”. However, these two different recessive syndromes are characterised by prenatal growth retardation, whereas birth weight is usually normal in Costello syndrome.

Pathogenesis

The pathogenesis of the disease is unknown. Similarities to leprechaunism have prompted authors to investigate the insulin receptor, but all results were normal. The apparent coarseness of the facies associated with hypertrophic cardiomyopathy suggests a storage disorder. However, there is no visceromegaly and the coarseness of the facial features is present from birth. Electron microscopy of the skin or liver has failed to show any storage material. Mucopolysaccharide and oligosaccharide screening were negative in all patients. Two single cases presented with sialuria, but these patients could have a similar but different condition. Morì et al. examined several tissues from two different patients under EM and found abnormalities consisting of fine, disrupted, and loosely constructed elastic fibres with hyperplasia of collagen fibres in the skin. The same authors observed calcifications and ballooning of the skeletal muscle fibres with infiltration of macrophages. These findings are in contradiction to repeated reports of normal EM findings. However, they represent an interesting clue to the pathogenesis of the disorder since they suggest a connective tissue disorder rather than a storage disorder.


