Congenital *Cutis Laxa* Associated with Growth Retardation

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ABSTRACT

Congenital cutis laxa *is a rare, clinically and genetically heterogeneous group of inherited disorders. It is characterized by degenerative changes in elastic fibres and manifests with skin laxity. Here we presented a six-month old boy with congenital* cutis laxa *associated with growth retardation. We reveal ultrastructural findings and discussed the differential diagnosis.*

Cutis Laxa Congénita Aociada con Retardo del Crecimiento

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RESUMEN

El laxa del cutis es un grupo raro, clínica y genéticamente heterogéneo de desórdenes heredados. Esta afección se caracteriza por cambios degenerativos en las fibras elásticas y se manifiesta en la hiperlaxitud de la piel. Aquí presentamos el caso de un niño de seis meses con cutis laxa *congénita asociada con retardo del crecimiento. Se revelan los hallazgos ultra-estructurales y se discute el diagnóstico diferencial.*

INTRODUCTION

Congenital *cutis laxa* (CCL) is a rare, clinically and genetically heterogeneous group of inherited disorders. It is characterized by degenerative changes in elastic fibres and skin laxity (1–3). In some cases, in addition to widespread laxity of the skin, involvement of the other organs, due to abnormalities in elastic tissue (4), is present. In CCL, two distinct patterns of inheritance have been clearly described: autosomal dominant (AD) and autosomal recessive [AR] (1–3, 5, 6). Cases that were previously described as X-linked recessive *cutis laxa* should now probably be classified as Ehlers-Danlos syndrome type IX (3, 7).

CASE REPORT

A six-month old boy presented to hospital with thin, pendulous, lax skin and growth retardation. The patient was the first child born, by Caesarean section at term, to a 24-year old mother and 25-year old father who were both healthy. The child had cyanotic skin and mucous membranes and he could not cry at birth. His birth weight was 2150g (small for gestational age) and birth length was 50 cm. His parents were not consanguineous. Tracing the family tree failed to identify *cutis laxa* in previous generations. His mother's antepartum history was unremarkable. When he was two months old, he was treated for bronchopneumonia thrice and operated on for bilateral inguinal hernias. In addition, he was diagnosed with congenital rickets and treated with vitamin D.

On physical examination, his weight, height and head circumference were 3100 g (below the 3rd percentile), 53 cm (below 3rd percentile), and 36 cm (below 3rd percentile), respectively. He was breastfed. Axillary temperature, pulse rate and blood pressure were 36°C, 140 beats/min and 90/54 mmHg, respectively.

Dermatologic examination showed flaccid, sagging cutaneous folds, particularly on the face, neck, abdomen and extremities Figs. 1, 2, 3. The skin was mildly erythematous, soft, velvety, movable and inelastic. The face revealed a wide nasal bridge, slightly everted nostrils, prominent ears, long philtrum, downward slanting palpebral fissures and sagging cheeks.

There was no hyperextensibility of the joints. His anterior fontanelle was wider than expected and he had no skeletal abnormality other than *pectus excavatum*. The corneas were clear and hair colour and texture were normal.

Cardiopulmonary examination revealed a systolic murmur. Echocardiography showed pulmonary hypertension. Radiographic examination of the gastrointestinal system and abdominal ultrasonography were normal. His mental development could not be evaluated due to his young age.

A skin biopsy was obtained and processed for light

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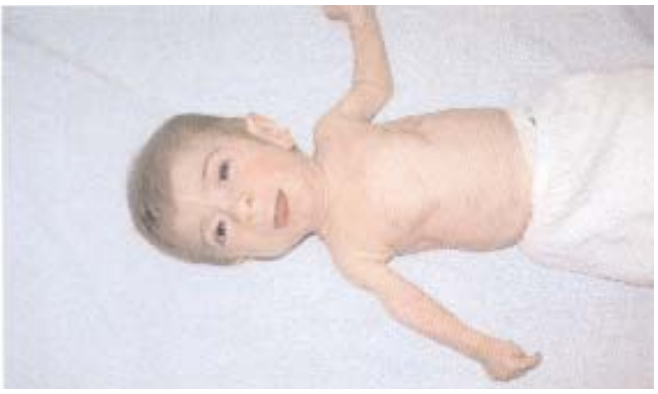

Fig. 1: A wide nasal bridge, slightly everted nostrils, prominent ears, downward slanting palpebral fissures, sagging cheeks and pectus excavatum are seen.

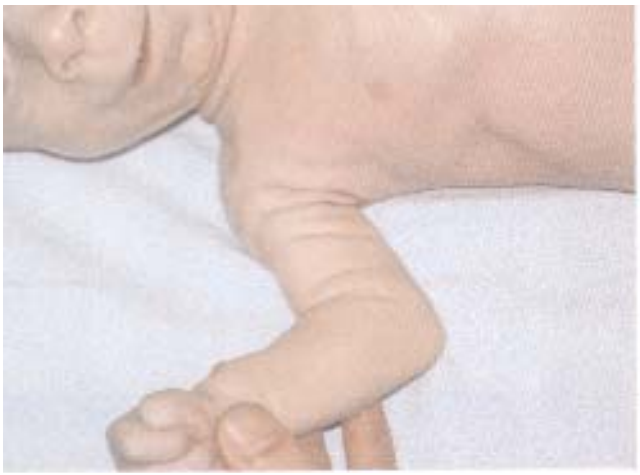

Fig. 2: Flaccid, sagging cutaneous folds, particularly on the neck and the extremities are seen.

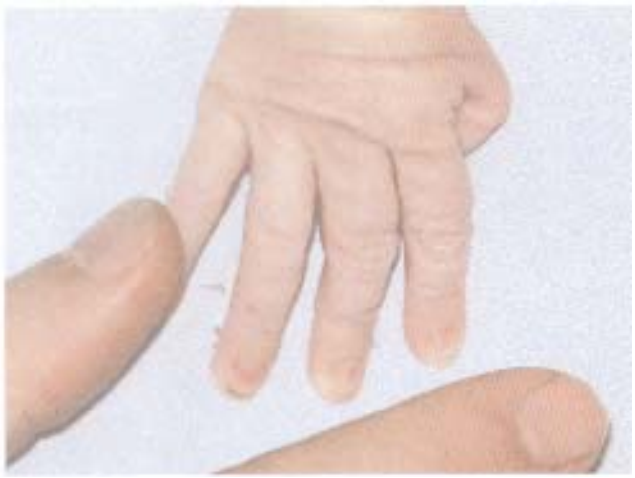

Fig. 3: Flaccid, sagging cutaneous folds on the hand are seen.

microscopy and electron microscopy. The histopathologic examination of the skin with haematoxylin and eosin stains showed that the epidermis had a normal structure with decreased rete ridges. The collagen bundles were stained homogeneously and were basophilic. The elastic fiber technique (Verhoeff) showed a decrease in the number of the elastic

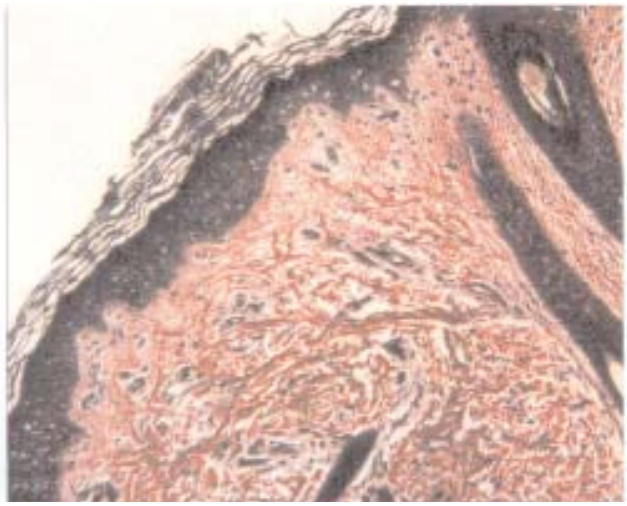

Fig. 4: Decrease in the number of the elastic fibers through the dermis is seen Verhoeff: X 20.

fibers (Fig. 4). Electron microscopy revealed few fragmented elastic fibers between dense collagen fibers (Fig. 5. 6). On the basis of these clinical and histopathological findings,

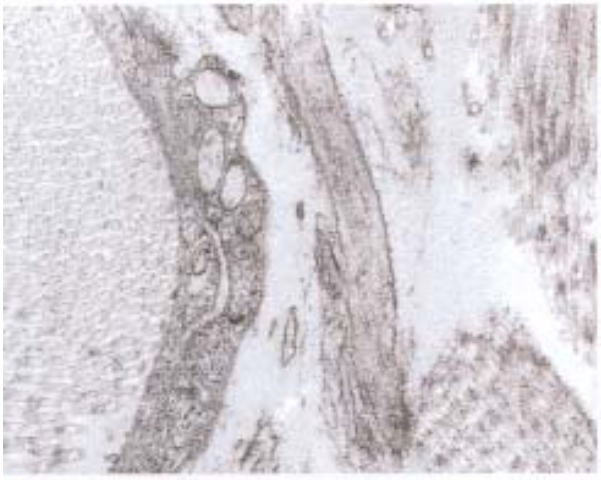

Fig. 5: Healthy elastic fiber structure is seen in control skin sample. TEM X 25.

a diagnosis of CCL was made.

DISCUSSION

The AD type of CCL presents in infancy or often in adulthood and tends to be relatively benign; it has no severe systemic manifestations but have mild cutaneous disease and cosmetic problems (2, 4, 6). A distinctive facies, inguinal hernia and bronchiectasis may be associated (4).

The AR form is more common, more severe and usually starts from birth (1, 2, 6). The internal organs are frequently involved due to fragmented and disorganized elas-

Fig. 6: Fragmented elastic fiber between dense collagen fibers is seen. TEM X 31.5.

tic fibre formation (1). Affected infants have an abnormal facies, generalized laxity of the skin, hernias, gastrointestinal and genitourinary tract diverticula, pulmonary emphysema, cor pulmonale, aortic aneurysm, dental caries, large fontanelles and osteoporosis (2, 6). An AR variety may be very severe with elastic tissue defects occurring in several organs, including fatal cardiopulmonary disease. Other manifestations include large ears and antimongoloid slanting of the palpebral fissures, dislocated hips, joint hyperextensibility, prolapsed rectal, vaginal or gastric mucosa, hernia and *pectus excavatum* (4).

Based on distinct clinical features, the AR type of CCL is divided into three subtypes. Autosomal recessive type I is associated with generalized findings including diaphragmatic hernia, diverticula of the gastrointestinal or urinary tract, pulmonary emphysema and cardiac involvement. These complications often lead to death during childhood. In AR type II CCL, the commonly described features include prenatal and postnatal growth retardation, delayed motor development, delayed closure of the large fontanelle, congenital dislocation of the hips and bone dysplasias. Autosomal recessive type III patients show severe mental retardation and corneal clouding due to degeneration of the Bowman membrane (2).

The index patient was the first child of non-consanguineous, healthy parents. He had markedly loose and wrinkled skin especially over the dorsum of the hands feet face and abdomen, *pectus excavatum*, large fontanelles, prominent ears, umbilical hernia, systolic murmur and delayed development. These findings and skin biopsy were consistent with *cutis laxa* syndrome, probably with type AR II CCL. Healthy parents despite a systemically affected infant may suggest an AR mode of inheritance. The presence of congenital rickets may also support this diagnosis.

To the best of our knowledge, there are few publications in the literature about *cutis laxa* associated with growth retardation (8–15). Two of them were reported from Turkey (8, 15).

An important diagnosis to be ruled out is the Ehlers-Danlos syndrome (EDS), in which the skin is not lax, but hyperelastic, resumes its normal position only slowly after being pulled out of position (4, 7). This disorder was not considered in this patient because there was no joint laxity, fragility or delayed wound healing.

Cutis laxa is a component of several genetic disorders. The most common ones among these rare disorders: Kabuki make-up syndrome, Costello syndrome, DeBarsy syndrome and Lens-Majewski hypertrophic dwarfism (16, 17).

Kabuki make-up syndrome is characterized by peculiar facial appearance, mental retardation, skeletal abnormalities, joint laxity, short stature, cardiovascular defects, genitourinary and gastrointestinal tract anomalies, otologic and ophthalmologic abnormalities and recurrent infections (17). Although mental development could not be assessed and chromosomal evaluation was not performed, absence of skeletal abnormalities, joint laxity, otologic or ophthalmologic abnormalities ruled out the diagnosis of Kabuki make-up syndrome.

Costello syndrome is emerging as a better delineated condition and should be included in the differential diagnosis of *cutis laxa* in association with postnatal growth retardation and developmental delay. Costello syndrome is an AD disorder characterized by soft, loose skin of the creases. The digits tend to be hyperextensible. Affected children develop papillomata around the nares, mouth and anal areas, and acanthosis nigricans in association with abnormal glucose metabolism occasionally. Although prenatal overgrowth and polyhydramnios occur, patients tend to have postnatal failure to thrive and a distinctive appearance. The facies are coarse with thick lips, macroglossia and relative macrocephaly. Severe short stature, mental retardation and hypertrophic cardiomyopathy are other associated manifestations (16). We ruled out that diagnosis due to the lack of prenatal overgrowth, hyperextensibility of digits, papillomata or distinctive facial appearance in the index.

DeBarry syndrome is an AR condition with *cutis laxa* in association with short stature, progeroid facies, frontal bossing, prominent nose and ears, cutaneous atrophy, hyperextensibility of small joints, choreoathetoid movements, corneal clouding due to degeneration of the tunica elastica of the cornea and severe mental retardation (3,16). The index case had no joint laxity, distinctive facial appearance or corneal clouding.

Cutis laxa has also been described in children with Lenz-Majewski hyperostotic dwarfism in association with syndactyly, brachydactyly, mental retardation, hypertelorism and enamel hypoplasia (16) which were not detected in our case.

The most important factor determining the prognosis in CCL is the involvement of internal elastic tissues, leading especially to pulmonary emphysema and cor pulmonale (3, 16). Prognosis depends on early diagnosis and treatment of systemic complications.

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