

Congenital cutis laxa syndrome: type II autosomal recessive inheritance

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Cutis laxa is a term that refers to markedly loose skin that is not hyperelastic. It is regarded as a genetically heterogeneous group of diseases and is presently divided into five types. We report a male patient with type II autosomal recessive disease.

The patient was the third child of first-cousin consanguineous, healthy parents. His two siblings died a few hours after birth. One of the siblings also had similar features and wrinkled skin. Our case had markedly loose and wrinkled skin especially over the dorsum of the hands and feet, and on the face and abdomen, dolichocephaly, hypertelorism, blepharochalasis, long philtrum, pectus excavatus, large fontanelles, prominent low-set ears and umbilical hernia. These findings and skin biopsy were consistent with cutis laxa syndrome. In addition to these findings, consanguinity, atypical facies, large fontanelles and umbilical hernia were typical manifestations of type II autosomal recessive cutis laxa.

Cutis laxa is a genetically heterogeneous group of connective tissue diseases characterized by skin that hangs in loose folds. The most apparent defect is loose, redundant, nonresilient skin, but systemic connective tissue abnormalities also exist, especially in conjunction with the early onset or autosomal recessive variety^{1,2}. Disorders with cutis laxa are presently divided into five types: an autosomal dominant type, an X-linked recessive type and an autosomal recessive type that is further divided into three subtypes³. A few dozen cases have been documented in the literature⁴.

We report a male patient with type II autosomal recessive disease.

Case Report

The patient was the third child of first-cousin consanguineous, healthy parents. The family history and pregnancy were unremarkable. His two siblings died a few hours after birth, cause unknown. As the parents expressed, one of them had a wrinkled skin. Birth weight, length and head circumference were 2700 g (3-10 p), 48 cm (25-50 p), and 34.5 cm (50 p), respectively. The

baby was admitted to newborn intensive care unit after birth and needed assisted ventilation for 13 days because of meconium aspiration and congenital pneumonia. He recovered from pneumonia, and his chest X-ray did not reveal emphysema. His physical examination revealed markedly loose and wrinkled skin especially over the dorsum of hands and feet, and on the face, neck, arms, legs, and axillary and inguinal areas (Figs. 1, 2). Facial manifestations were dolichocephaly, deep-set eyes, hypertelorism, blepharochalasis, long philtrum, short columella, anteverted nares, low-set ears and long earlobes (Fig. 3). Also, large fontanelles (4x5 cm), bilateral palmar Simian creases, pectus excavatus, and bilateral inguinal and umbilical hernia were noted (Figs. 1, 2). Radiological examination was unremarkable. Abdominal ultrasonography (US) revealed the right renal pelvis to be minimal ectatic. Cranial US was normal. No congenital hip dislocation or corneal clouding was noted.

Skin biopsy revealed hyperkeratosis, absence of elastic fibers of upper dermis, and irregularly shaped elastic fibrils of mid-dermis that manifested no evidence of maturation (Figs. 4,



Fig. 1. Note the loose and wrinkled skin on the face, neck, arms, legs, and axillary and inguinal areas and umbilical hernia.

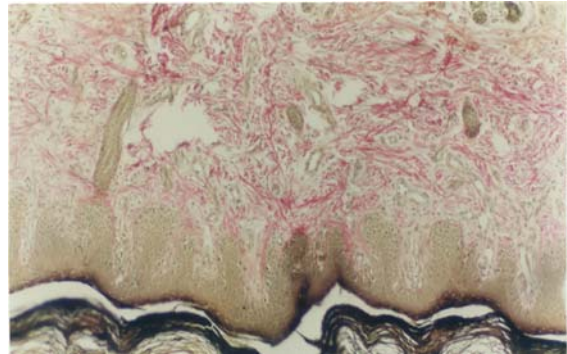


Fig. 4. Hyperkeratosis, normal epidermal structure and edema of upper and mid-dermis are seen. Elastic fibers are reduced in number while collagen is normal.



Fig. 2. Axillary wrinkled skin, pectus excavatus and dolichocephaly are shown.

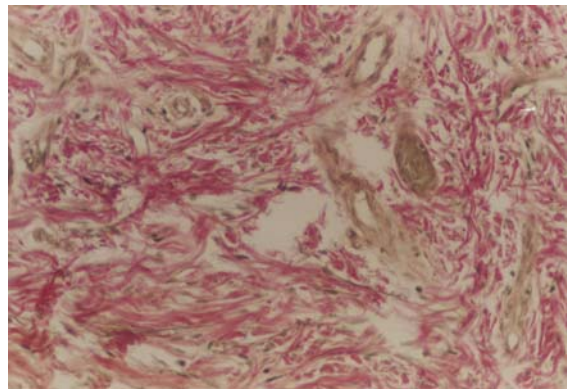


Fig. 5. Skin biopsy reveals absence of elastic fibers of upper dermis, and irregularly shaped elastic fibrils of mid-dermis that manifest no evidence of maturation.



Fig. 3. Facial manifestations are deep-set eyes, hypertelorism, blepharochalasis, long philtrum, short columella, anteverted nares, low-set ears and long

5).

Ichthyosis was not considered since an apparent granular layer was present in epidermis. These biopsy findings were compatible with cutis laxa syndrome.

When he was seen again at two months of age, postnatal growth retardation was remarkable. Weight, length and head circumference were 3300 g (3rd p), 51 cm (<3rd p), and 35 cm (<3rdp), respectively. At three months of age he died at home, cause unknown, presumably because of respiratory distress.

Discussion

Cutis laxa syndromes all have distinct manifestations. One genetic form is a benign autosomal dominant inheritance with variable penetrance, and another form has malignant autosomal recessive inheritance. These have not yet

been completely delineated⁵. The autosomal dominant type that is not associated with mental retardation is the most common type. Dermis is prominently involved, and when pulmonary insufficiency and other internal manifestations are not present, the prognosis with this type of cutis laxa is good. This systemic disease has a reduction of elastin fibers with laxity of the skin, which hangs in loose folds in all areas, as in other cutis laxa syndromes. Deepening of the voice is characteristic. Dermal changes are usually apparent at birth or develop during infancy. These changes may remain static or may progress^{1,3,4,6}.

The X-linked recessive type is reported to result from deficiency of lysyl oxidase, an extracellular copper enzyme, the gene for which is located on chromosome 5^{7,8}. Affected patients show exostosis and bony horns on each side of the foramen magnum^{4,7}. This variant of cutis laxa is presently grouped with other disorders of copper transport.

Mental retardation and growth delay are associated with the autosomal recessive (AR) types of cutis laxa^{5,9}. They are presently divided into three subtypes. AR type I, a severe, lethal form is associated with generalized disorders including cardiac and pulmonary involvement, multiple hernia, and diverticula of the gastrointestinal or urinary tract. Bad prognosis is usually due to early onset of pulmonary emphysema. AR type III shows severe mental retardation, prenatal and postnatal growth retardation, cutis laxa and corneal clouding. AR type II includes prenatal and postnatal growth retardation, delayed motor and mental development, cutis laxa, delayed closure of large fontanelles, multiple hernia, kyphosis, scoliosis, pectus excavatus and congenital hip dislocation. Significant facial manifestations are dolichocephaly, antimongoloid slant, long philtrum, blepharochalasis, upturned nares, depressed nasal bridge, hypertelorism, low-set ears, and long earlobes. Palmar Simian creases are also noted^{3,4,6,10}. The patient described here had manifestations very similar to those in type II AR cutis laxa. Postnatal a growth retardation, multiple hernia, large fontanelles and typical facies were the characteristic features of type II AR cutis laxa. Consanguinity and death of a sibling with the same features support autosomal recessive inheritance. IN the reported

cases, the ratio of males to females is 5 to 14⁵. The etiology of this disorder is unknown. The electron microscopic examination of skin shows that elastic fibrils in papillary and reticular dermis vary in content, appearance, and maturation¹¹. Light microscopy also reveals a decrease in the number, fragmentation and disorderly arrangement of elastic fibers^{1,12-14}. In our case skin biopsy revealed hyperkeratosis, absence of elastic fibers of upper dermis and irregularly shaped, immature elastic fibrils of mid-dermis.

Costello syndrome, which should be included in the differential diagnosis of cutis laxa, has distinctive features such as nasal papillomata, coarse facies and mental retardation^{15,16}. Ehlers-Danlos syndrome type VII C, which was first described in 1992 and is characterized by dermatoparaxis, should also be included in the differential diagnosis of cutis laxa¹⁷. Although similar atypical facies and cutis laxa are seen in both syndromes, electron microscopic studies of collagen fiber abnormalities and features such as short limbs, hirsutism, extreme skin fragility and easy bruisability are not present in cutis laxa syndrome¹⁷. Cutis laxa AR type II is known to be a rare disorder; however, nine cases from our country have been reported who had syndrome of congenital cutis laxa with ligamentous laxity and delayed development^{9,18-23}.

The gene responsible for this type of cutis laxa demonstrates pleiotropy. Prenatal diagnosis of congenital cutis laxa remains elusive because the underlying defect leading to a lack of proper elastin assembly is unknown. Skin biopsy would be of little help for that purpose since elastic fibers become evident only in the late second trimester of pregnancy¹⁴.

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