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(CASE REPORT)

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Congenital Cutis laxa: Two pediatric cases

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Abstract

The Cutis laxa syndrome is a group of rare heterogeneous disorders of the elastic tissue characterized mainly by wrinkled, loose skin giving an aged appearance, which may be associated with skeletal abnormalities, developmental abnormalities, and even severe systemic involvement.

Cutis laxa syndrome (CL) is either acquired or congenital. There are several forms of congenital cutis laxa distinguished according to the mode of transmission, the extent of visceral involvement, associated anomalies, and the severity of the disease: autosomal dominant CL, autosomal recessive CL, X-linked CL.

In the light of data from the medical literature and through the observation of 2 sisters followed up in a pediatric dysmorphology consultation for congenital cutis laxa, the authors underline the clinical, paraclinical, etiogenotypic, therapeutic, and evolutionary peculiarities of this rare disease.

Keywords: Cutis laxa; Genetic transmission; Hyperlaxity skin; Histological analysis

1. Introduction

Cutis laxa is a relatively rare condition, affecting both boys and girls.

Its frequency is not well known. According to the medical literature, there are fewer than 1000 cases worldwide [1]. Cutis laxa is characterized by an aspect of premature senescence, of skin hyperlaxity associated with variable systemic manifestations. They can be congenital or acquired [2].

In this study, we report the observation of two sisters followed up in our pediatric clinic for dysmorphic syndrome.

2. Case presentations

2.1. First case

A female child was born on 17 June, 2011, the eldest of two siblings, of first cousin parents with no phenotypic abnormalities of Cutis laxa. Her birth weight was 2900g, with no history of similar cases in the family, with good psychomotor development, who presented with dysmorphic syndrome at birth.

The clinical examination found at the time of the consultation at the age of 8 years an old aspect of the face, a loose and elastic skin, wrinkled, distant antimogoloid eyes, large ears, normo-implanted but unstuck, a small jaw with dental caries, ogival palatal vault, a delayed staturo-weight: a weight of 16 kg (-2DS) and a height of 1 m10 (-2DS), walking

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normally, no articular hyperlaxity nor other osteoarticular attacks. On ophthalmological examination, myopia with a visual acuity of 6/10 for both eyes was found with no cataract. The rest of the clinical examination was normal. Complementary examinations, including a chest X-ray, an ionogram, CRP, a cardiac ultrasound, and a skeletal X-ray, were normal.

A skin biopsy with histological study was performed, showing decreased, damaged, and distorted elastic fibers in the dermis after orcein staining. Collagen fibers stained with hematoxylin-eosin showed no signs of inflammation. This confirms the diagnosis of cutis laxa.

Figure 1 Image of our child suffering from cutis laxa

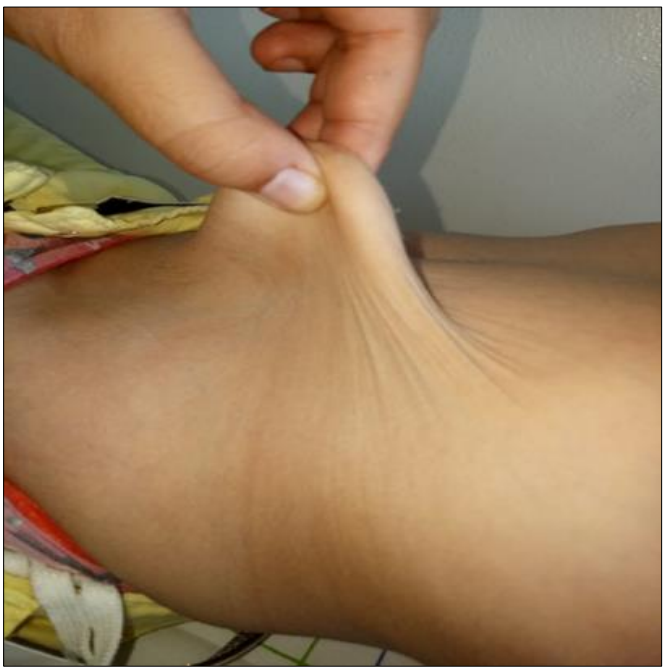

Figure 2 Image showing hyperlaxity of the skin in our patient

2.2. Second case

The second case is the youngest sister of the first patient, born on January 23, 2014, with a birth weight of 3250g and with delayed psychomotor development: sitting at age 1 year old, walking alone at age 2 years old.

Clinical examination at the age of 5 years found excessive laxity of the skin forming flaccid folds giving a senile appearance, a long face, hypertelorism of the eyes, a small jaw and dental carries, high arch of the palate, with onychomycosis on both feet, a delay in weight of 8 kg (-2DS) and height of 1 m (-2DS), and the ability to walk normally without joint hyperlaxity or other osteoarticular damage. On ophthalmological examination, myopia with a visual acuity of 7/10 for both eyes was found with no cataract. The rest of the clinical examination was normal. Complementary examinations, including a chest X-ray, an ionogram, CRP, a cardiac ultrasound, and a skeletal X-ray were-normal. A skin biopsy was not performed on our patient.

3. Discussion

Cutis laxa is a rare disease of skin elasticity, giving the appearance of premature aging, contrasting with the physiological age of the patient. Histological examination shows a decrease and disorganization of the elastic fiber network of the dermis. Collagen may be normal or altered, which is the case of our two patients [3].

The systemic involvement of cutis laxa conditions the vital prognosis and can lead to pulmonary involvement (pulmonary emphysema, bronchiectasis), cardiovascular involvement (aneurysms, sinuous arteries, valve abnormalities), digestive involvement (diverticula, hernias), and orthopedic involvement (joint laxity, bone abnormalities, dislocation).

However, the determination of the precise form can only be done according to the family history and the symptoms present in the patient, and allow us to distinguish between the acquired and congenital form [4].

Acquired Cutis Laxa: Adults are the most commonly affected by Acquired Cutis Laxa. Although the cause is unknown, it has been observed in some individuals after certain environmental exposures, such as certain medications, infections, or autoimmune diseases. Acquired Cutis laxa is not genetically transmitted. However, one focus of Dr. Zsolt Urban's research is to determine if some individuals may have a genetic predisposition to develop Cutis laxa after certain exposures.

Acquired Cutis laxa is not genetically transmitted. However, there may be a genetic predisposition to develop Cutis laxa after certain exposures [5].

Several different forms of cutis laxa have been described and are distinguished according to the mode of transmission, extent of visceral involvement, associated abnormalities, and severity of the disease.

3.1. Autosomal dominant Cutis laxa

Cutaneous manifestations are present from birth or during infancy. The visceral manifestations are absent or moderate and include pulmonary lesions (pulmonary emphysema, bronchiectasis), cardiac lesions (aortic aneurysm, right ventricular hypertrophy), digestive hernias, and genital prolapses, but generally have a good prognosis. The genetic anomaly responsible is a mutation of a gene (elastin gene ELN) [6, 7].

3.2. X-linked cutis laxa

A rarer form, also known as occipital horn syndrome, presents with skin involvement, facial dysmorphia with occipital exostoses forming horns, sinuous carotid arteries and intracranial arterial stenoses, urinary tract stenoses and diverticula, ligament hyperlaxity, mental retardation, and growth retardation. It is associated with mutations in the ATP7A gene [8].

3.3. Autosomal recessive cutis laxa

The most frequent. There are 3 forms of autosomal recessive cutis laxa, themselves further divided into additional subtypes:

3.3.1. Cutis laxa I

Cutis laxa I A

Due to mutations in the Fibulin 5 gene, it is characterized by loose skin, hernias, and lung damage such as emphysema from an early age.

Cutis laxa I B (CL1B)

Due to mutations in the Fibulin 4 gene, CL1B is characterized by loose skin associated with damage to the cardiovascular system (tortuosity, aneurysms, stenosis), the skeleton (joint laxity, long and thin fingers, hernias, and bone fragility) and morphological features involving the face (small chin, high palate, widely spaced eyes).

CL1B can be very severe, with a very short life expectancy after birth.

Cutis laxa I C

Also known as Urban-Rifkin-Davis syndrome due to mutations in the LTBP4 gene, is characterized by loose skin, associated with severe pulmonary, gastrointestinal, and urinary problems.

3.3.2. Cutis laxa II

Cutis laxa II A

Due to mutations in the ATP6V0A2 gene, is characterized by senile, wrinkled skin involving the entire body that improves with age, enlarged anterior fontanel; dislocation of the hips at birth, hernias, and severe myopia and developmental delay. These features overlap with those of Wrinkly Skin Syndrome, which causes wrinkled skin, microcephaly, and mental retardation, as well as muscle and bone problems, and is caused by mutations in the same ATP6V0A2 gene.

Cutis laxa II B

As a result of PYCR1 gene mutations. Affected individuals have loose skin, giving an aged appearance, delayed growth and development, bone and joint damage; microcephaly; a large forehead; a triangular face; and large ears.

Cutis laxa III or De Barsy syndrome

Is due to mutations in the PYCR1, ATP6V0A2, or ALDH18A1 genes. It has a common phenotype with Cutis laxa IIA and IIB. Causes growth retardation, moderate to severe mental retardation, cataracts, and joint laxity. Other skin problems associated with loose skin contribute to an aged appearance. Typically, it has no cardiovascular or pulmonary symptoms[9,10].
The prognosis for Cutis laxa varies depending on the form of the disease. The effects can be mild and some individuals have a near-normal life, while for others, the disease can be fatal [11].

The association described in our two patients corresponds to an autosomal recessive form of cutis laxa type III, which is considered because of the consanguinity of the parents who are of normal phenotype and the absence of visceral damage.

The fact that the daughters are affected by Cutis laxa rules out the probability of X-linked hereditary transmission.

Some syndromes are difficult to differentiate from cutis laxa, including:

- **The Ehlers-Danlos syndrome (EDS)**

EDS is a heterogeneous group of inherited connective tissue disorders, comprising 9 distinct types with variable prognosis. Due to mutations in collagen genes (COL5A1, COL5A2, COL3A1, COL1A1) and enzymes (lysyl hydroxylase, procollagen Npeptidase).

There is some difference between EDS and CL: clinically, hyperelasticity of the connective tissue and impaired wound healing are opposed to the inelasticity that characterizes CL. Histologically, there are changes in the collagen fibers, which are rarefied and disorganized. Joint hyperlaxity is often present [12].

- **Costello Syndrome**

This is a syndrome that involves severe postnatal growth retardation and flabby, hyperelastic, and papillomatous skin. Affected children have a slight psychomotor delay.

It is a very rare syndrome; only nine cases are published in the literature.

Histologically, there is a fragmentation of the elastic fibers with a lack of anastomotic points, an ultrastructural aspect related to that of congenital cutis laxa. The two conditions may have a common pathogenesis [13, 14].

- **Heritary osteodysplastic geroderma (HOG)**

Affected subjects have a small stature with a characteristic face: a pointed nose, hanging cheeks, and large ears.

The skin shows diffuse, atrophic folds, more pronounced on the extremities, neck, and abdomen. The venous network is visible.

HOG is associated with bone abnormalities such as generalized osteoporosis, platyspondyly, deformities of the spine, and epiphyseal abnormalities of the long bones.

We can also see hyperlaxity of the hands and feet, as well as congenital hip dislocations.

These clinical anomalies are also present in CLC Type III and cutis laxa secondary to SED III and VII.

Histologically, there is fragmentation of elastic fibers.

This syndrome is hereditary and of unknown molecular mechanisms [15].

- **Progeria**

The general appearance of these children is reminiscent of an old man; thinning, wrinkled skin, pressed directly against the underlying muscles, which may appear falsely hypertrophied due to the absence of the adipose pannicle. Delayed closure of the fontanelles and bone demineralization can be found [16].

4. Conclusion

Cutis laxa is an exceptional condition characterized by clinical and genetic polymorphism, requiring multidisciplinary management to ensure adequate follow-up.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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