

## Classic Ehlers-Danlos syndrome: Case Report and Brief Review of Literature

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**SUMMARY** Easy bruising in children represents a diagnostic conundrum. Although trauma (accidental or not) and bleeding disturbances are the most common causes, other rarer etiologies should be considered in differential diagnosis. When a 4-year-old male patient presented with a history of bruising and hematomas after slight injuries, coagulopathy and physical abuse were suspected. However, the presence of skin hyperextensibility, generalized joint hypermobility, atrophic and "cigarette paper" scars, *pes planus*, piezogenic pedal papules, and similar clinical picture in the mother, maternal uncle and grandfather suggested a diagnosis of Ehlers-Danlos syndrome, classic type. Genetic study revealed a heterozygous variant (c.379C>T) in exon 3 of the *COL5A1* gene, not previously described in the literature, confirming the clinical suspicion. The authors intend to draw attention to this rare and diagnostically challenging condition that should be correctly diagnosed for the early adoption of preventive measures.

**KEY WORDS:** Ehlers-Danlos syndrome, classic Ehlers-Danlos syndrome, skin hyperextensibility, joint hypermobility, easy bruising

### INTRODUCTION

The Ehlers-Danlos syndromes (EDS) are a heterogeneous group of disorders characterized by joint hypermobility, hyperextensible skin, and fragile tissues that are extremely susceptible to trauma (1). As many as 1 in 5000 individuals may be affected by some form of the disease (2). The latest classification of EDS, The Villefranche Nosology (3), recognizes six subtypes for

which major and minor diagnostic criteria have been defined. Categorization is based on clinical and corresponding molecular pathogenetic findings in collagen types I, III and V, or processing enzymes. The classic form of EDS is one of the most common, occurring in 1 per 10,000 to 20,000 infants (2). It includes two previously designated subtypes (EDS type I, or *gravis*,



**Figure 1.** Clinical appearance of the patient: extensive bruising, and atrophic and “cigarette paper”-like scars on the anterior aspect of the legs (A), skin hyperextensibility (B and C), and generalized joint hypermobility (D, E and F).

and EDS type II, or *mitis*) that are now recognized to form a continuum of clinical findings and differ only in phenotypic severity (2,4-6).

### CASE REPORT

A 4-year-old male patient (index case), born at term to non-consanguineous healthy parents, was referred to the Pediatrics Department due to easy bruising and hematomas after trivial injuries, located at lower limbs, since his first year of life. There were no other complaints, and antenatal and perinatal histories were irrelevant. At physical examination, extensive bruises were observed on the shins, some associated with subcutaneous nodules (Fig. 1A). Coagulopathy and child abuse were suspected, but initial investigations, including hemogram, basic biochemical profile, complete coagulation study and radiog-

raphy of the lower limbs, revealed no changes, and social assessment did not support the suspicion of physical abuse. The child was therefore evaluated by a dermatologist. A skin biopsy was non-contributory, however, attentive cutaneous examination revealed additional findings besides maintenance of bruising, namely skin hyperextensibility (Fig. 1B, C), soft, velvety skin, atrophic, darkly pigmented and “cigarette paper”-like scars, *pes planus*, and piezogenic pedal papules. Generalized joint hypermobility was present (Beighton score 8/9) (Fig. 1D-F). When asked, the mother referred similar clinical features in herself, her brother, and her father. The diagnosis of classic EDS was likely. Echocardiogram and abdominal ultrasonogram were normal. Biochemical analysis of the electrophoretic pattern of the (pro)collagen type I, II and V proteins, secreted in the medium as well as retained

**Table 1.** Diagnostic criteria of classic Ehlers-Danlos syndrome. Adapted from Beighton *et al.* (3) and Malfait *et al.* (5)

Major criteria	Minor criteria
<ul style="list-style-type: none"> <li>• Skin hyperextensibility*</li> <li>• Widened atrophic scarring (a manifestation of tissue fragility)</li> <li>• Joint hypermobility†</li> <li>• Positive family history</li> </ul>	<ul style="list-style-type: none"> <li>• Smooth, velvety skin</li> <li>• Molluscoid pseudotumors (fleshy, heaped-up lesions associated with scars over pressure points such as the elbows and knees)</li> <li>• Subcutaneous spheroids (small, hard cyst-like nodules, freely moveable in the subcutis over the bony prominences of the legs and arms, which have an outer calcified layer with a translucent core on x-ray)</li> <li>• Complications of joint hypermobility (e.g., sprains, dislocations/subluxations, and <i>pes planus</i>)</li> <li>• Muscle hypotonia, delayed gross motor development</li> <li>• Easy bruising</li> <li>• Manifestations of tissue extensibility and fragility (e.g., hiatal hernia, anal prolapse in childhood, and cervical insufficiency)</li> <li>• Surgical complications (postoperative hernias)</li> </ul>

A combination of 3 major diagnostic criteria is highly specific for the presence of the condition. The presence of one or more of minor criteria contributes to the diagnosis of classic EDS, but is not sufficient to establish the diagnosis; \*skin hyperextensibility should be tested at a neutral site, such as the volar surface of the forearm; †joint hypermobility in classic EDS is generalized, affecting both large and small joints and can range in severity from mild to severe. It should be assessed using the Beighton scale, the most widely accepted grading system for the objective semiquantification of joint hypermobility.

in the cell-layer showed a normal profile. However, sequence analysis of the entire coding region (exons 1-66) and all intron-exon boundaries of the *COL5A1* gene identified a heterozygous variant (c.379C>T) in exon 3, not previously described in other patients or in controls, confirming the clinical suspicion. The patient was referred for Pediatric Cardiology and Ophthalmology consultations, where to date no changes have been detected.

## DISCUSSION

Ehlers-Danlos syndrome, classic type is a disorder of connective tissue inherited in an autosomal dominant manner. It is estimated that approximately half of affected individuals have inherited the disease-causing mutation from an affected parent, and the other half have a *de novo* mutation (5,6). Mutations in the *COL5A1* and *COL5A2* genes, encoding the  $\alpha 1$  and  $\alpha 2$ -chain of type V collagen, respectively, are identified in about 50% of patients with a clinical diagnosis of classic EDS (7). It is estimated that 46% of cases of classic EDS can be attributed to mutations in *COL5A1* and 4% to mutations in *COL5A2* (6,7). Most mutations identified result in a reduced amount of type V collagen in the connective tissues available for collagen fibrillogenesis (4). Considerable inter- and intrafamilial differences in the phenotypic expression are observed in classic EDS, but no genotype-phenotype

correlations can be made so far (4). Our case reflects a dominantly inherited mutation transmitted from the grandfather to his daughter, son and grandson (index case). The c.379C>T variant identified in *COL5A1* gene have not been previously described in the literature. It is a nonsense variant predicted to lead to the substitution of glutamine into a premature stop codon on position 127 (p.Gln127STOP). This variant may result in a truncated *COL5A1* protein or diminished *COL5A1* mRNA due to mRNA decay. Due to its truncating nature, it was considered pathogenic, confirming the clinical diagnosis.

Classic EDS is characterized by hyperextensible and fragile skin, which is smooth and velvety to the touch, delayed wound healing with formation of atrophic scars, easy bruising, and generalized joint hypermobility (4,5). The skin manifestations can vary in severity from mild to severe; milder forms were previously termed the *mitis* type, or EDS type II (4,5). Traumatic or surgical scars are thin, papyraceous, and may stretch considerably after healing. In more severe cases, scars may have a characteristic "fish mouth"- or "cigarette paper"-like appearance. Thin, atrophic, darkly pigmented scars are formed as a consequence of intradermal or subdermal hematomas, and occur mainly at pressure points. As observed in our patient, affected persons may have pressure-induced herniation of subcutaneous fat on the wrists

**Table 2.** Preventive, therapeutic and surveillance measures in classic Ehlers-Danlos syndrome (4,5)

- Wearing pads or bandages over the forehead, knees, and shins to avoid skin tears – young children with skin fragility
- Wearing soccer pads or ski stockings with shin padding during activities – older children
- Ascorbic acid (vitamin C) to reduce bruising; in general, a dose of 2 g/day is recommended for adults, with proportionally reduced doses for children
- Avoid acetylsalicylate (aspirin) and sports that strain joints (contact sports, fighting sports, football, running)
- Physiotherapy for children with hypotonia and delayed motor development
- Promotion of muscle strength and coordination with non-weight-bearing exercise, such as swimming
- Anti-inflammatory drugs to alleviate arthralgias
- Adapt lifestyles in patients with hypotonia, joint instability and chronic pain
- Close dermal wounds without tension, preferably in two layers; apply deep stitches and left skin stitches in place twice as long as usual; carefully tape the borders of adjacent skin to prevent stretching of the scar
- Treat cardiovascular problems
- Yearly echocardiogram when aortic dilatation and/or mitral valve prolapse are present
- Refer pregnant women with EDS to high-risk obstetric practices when possible because of increased pregnancy risks

or on the medial or lateral aspect of the heels, evident when the patient is standing (piezogenic pedal papules). A comprehensive and thorough description of other findings described in patients with classic EDS can be found elsewhere (3-5). Diagnostic criteria of this subtype of EDS were developed by a medical advisory group at a conference in Villefranche in 1997 (3) (Table 1). Our patient fits all the major criteria and three of the minor criteria.

The diagnosis of EDS, classic type is established by clinical examination, family history and identification of mutations in *COL5A1* or *COL5A2* (4). In patients in whom classic EDS is suspected, collagen protein analysis can be performed on cultured fibroblasts derived from a skin biopsy to obtain the source of protein for electrophoretic analysis of collagen types I, III, and V (4,5). However, because type V collagen is synthesized by fibroblasts at low levels, alterations in electrophoretic mobility are poorly reproducible, making it an ineffective method for routine diagnostic evaluation (7). The test, however, helps exclude other subtypes of EDS. Light and electron microscopy of a skin biopsy, in classic EDS, often reveal changes in the arrangement, diameter and outline of collagen fibers suggestive of disturbed collagen fibrillogenesis (8). Prenatal diagnosis and preimplantation genetic diagnosis for pregnancies at increased risk may be possible for families in which the disease-causing mutation has been identified in an affected family member (4-6).

Other types of EDS should be considered in individuals with easy bruising, joint hypermobility, and/or chronic joint dislocation (4,5). Moreover, classic EDS shows limited overlap with other disorders, including Marfan syndrome, occipital horn syndrome (formerly known as EDS type IX), cutis laxa syndromes, De Barsy syndrome, Loeys-Dietz syndrome, Larsen syndrome,

Menkes disease and osteogenesis imperfecta, but these conditions are differentiated by other distinctive clinical features (4-6). As observed in our patient, classic EDS may also be mistaken for bleeding disturbances or child abuse in the setting of extensive bruising and/or bizarre skin scars.

No treatment for the underlying defect is presently available for EDS. However, a series of preventive guidelines are applicable (Table 2).

## CONCLUSION

With this case, the authors intend to draw attention to the clinical diagnosis of EDS as the skin and joint findings, often undervalued, can be the reflection of a major systemic pathology. The true prevalence of classic EDS is difficult to establish because some individuals with milder manifestations of the disease, especially those previously classified as EDS type II, rarely seek medical care and, consequently, go undetected. Therefore, a high index of suspicion is required for the early diagnosis of such a forgotten entity.

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