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Research

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Clinical and Ultrastructural Skin Alterations in the Ehlers-Danlos Syndrome, Hypermobility Type

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ABSTRACT

Ehlers-Danlos Syndrome (EDS) represents a cluster of specific genetic connective tissue disorders. It is clinically evoked when skin appears velvety and hyperextensible, in combination with joint laxity and connective tissue fragility. The hypermobile variant (EDSH) is among the most common presentations. It presents as an autosomal dominant pathology. The genetic mutation presently remains undisclosed in most cases. However, ultrastructural alterations are often distinguishable. Ehlers-Danlos Syndrome Hypermobile (EDSH) is mostly observed in women in whom additional signs to joint laxity are present. Hyperextensibility and/or velvety presentation of skin is one of the two major diagnostic signs in EDSH. Atrophic scars and delayed wound healing are commonly present. These features have to be considered in particular by plastic surgeons. The ultrastructural skin changes show various numbers of flower-like collagen fibres as well as other abnormalities in the connective tissue components.

KEYWORDS: Collagen; Elastic fibre; Ultrastructure; Tenascin; Decorin.

INTRODUCTION

Ehlers-Danlos Syndrome (EDS) encompasses an heterogenous cluster of connective tissue disorders, currently classified into six principal types.[1,2] They are characterized by variable combinations of increased skin distensibility and elasticity, joint laxity and connective tissue fragility. The Ehlers-Danlos Syndrome Hypermobile (EDSH) type is probably the most frequent entity. It is perceived as an autosomal dominant disease, although women are more frequently affected than men.[3-5] This condition remains difficult to diagnose due to variable clinical expressions, the largely undisclosed genetic origin, and the possible correction in joint laxity during aging and various degenerative disorders. Somewhat EDSH is clinically identified by joint laxity, and moderate skin hyperextensibility. It is frequently observed in association with delayed wound healing and atrophic scar development**.** Curative surgery and more often corrective esthetic surgery are concerned by these skin complications in EDSH women.

Collagen and elastic fibres are major extracellular matrix fibrous structures of the dermis. Other molecular components contribute to the overall mechanical properties of the skin. The main non-collagenous molecules of the dermis are the proteoglycans corresponding to a core protein and a covalent carbohydrate. Two major proteoglycans are found in the extracelllar matrix of the dermis. Versican is a large proteoglycan which belongs to the lectican family prone to bind hyaluronic acid. In contrast decorin is a small leucine-rich proteoglycan representing about 30-40% of the total proteoglycans of the skin. Decorin plays a key role in fibrogenesis and functional organization of the skin connective tissue. Tenascin X (TNX) is a minor component of connective tissue and appears to regulate the assembly of collagen.

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EDSH AND WOMEN

EDSH is disclosed more frequently in women than in men.[3-5] Indeed, a study showed that the sex ratio reached 43 women (84%) for 8 men (16%).[4] In our experience from 156 Caucasian patients, we shared a similar gender distribution with 131 (84%) women, aged 10-65 year-old, and 25 (16%) men, aged 9-67 year-old. Only 8/25 (36%) men, aged 9-26 year-old, compared to 102/131 (77,8%) women, aged 10-58 year-old, had a Beighton score above 5/9. The 15/25 men, aged 32-67 year-old, and 29/131 women, aged 42-65 year-old, had a lower Beighton score under 5/9, and they presented with complications of joint laxity including chronic joint pains, joint dislocations, sprains, (sub)luxations, tendinitis, hyperextensibility and/or velvety skin and positive familial history.

The gender difference in EDSH prevalence is in part related to distinct articular pain perception[6,7] and in musculature which are influenced by sex hormones.[4] The presence of estrogen receptors in ligaments,[8] as well in tenocytes[9] and muscles[10] suggests that estrogens play a role in the metabolism of these structures. Hormone replacement therapy in menopausal women improves skin and tendon elasticity and muscle performances.[11-13] These observations suggest a role of estrogens on the skeletal muscular system and explain that joint laxity is more notified in women.

DIAGNOSTIC CRITERIA

The EDSH diagnosis[1,2] is rooted on the presence of one or two major criteria including hyperextensible and/or velvety skin, and generalized joint laxity. This latter aspect is assessed according to the Beighton score reaching 5/9 or more defining joint hypermobility. The global score is calculated by adding each single joint mobility obtained by passive dorsiflexion of the little fingers beyond 90°, passive apposition of the thumbs to the flexor aspect of the forearm, hyperextension of the elbows and knees beyond 10°, and flexion of the trunk with the knees extended, and the hands flat on the floor. Skin hyperextensibility is assessed by pulling up the skin on the volar aspect of the forearm until resistance is felt. Skin must return to its original position without transient redundant folds. More precise information is obtained by objective measurements of the mechanical properties of skin.[14,15]

The minor diagnostic criteria for EDSH are recurring joint dislocations, chronic joint/ limb pain and positive family history. A minor criterion is just suggestive of the diagnosis.

In the Caucasian population the overall prevalence of EDS is assessed in the range from 1/5,000 to 1/1,000,000 births. Clearly, such estimation differs according to the EDS type. The rates are commonly higher for Blacks. Some EDS patients are identified by molecular biology particularly when the EDS types are characterized by a single defined and specific genetic mutation. Mutations in collagen I, III and V have been identified, but non-fibrous connective tissue components including TNX and decorin are also involved in various EDS types. However, some EDS clinical types are associated with a few distinct molecular alterations. Furthermore, a set of EDS types share similar gene mutations. Still other clinical variants have not been identified by molecular means. Therefore, such molecular methods are not fully satisfactory for routine identification of each EDS case.

In EDS classic type, most of the mutations are disclosed in *COL5 A1* and *COL5 A2* genes with some exceptions related to COL1 and TNX mutations. Hypermobile EDS, and its related condition called the family benign joint hypermobility syndrome, appear commonly as an underdiagnosed EDS hypermobile type. Sporadic mutations, including *COL5 A1* and *TNX-B* haploinsufficiency, were reported in a few cases of hypermobile EDS, but mutations remain undisclosed in most cases. The EDS vascular type is caused by type III procollagen gene (*COL3 A1*). Distinct other EDS types represent scarities.

CLINICAL MANIFESTATIONS

Beyond the classical diagnostic criteria, EDSH presents several other clinical manifestations including gyneco-obstetric, neurologic, cardio-pulmonary and gastrointestinal features.[16-21]

In EDSH, skin hyperextensibility is variable, and usually discrete compared with the EDS classic type.[15] Measurements of the skin mechanical properties provide an objective evaluation of the cutaneous hyperlaxity.[14,15,22] Other cutaneous signs are possibly observed, including delayed wound healing, and atrophic enlarged scars (Figure 1), but not molluscoid pseudotumors associated with papyraceous scars as seen in the EDS classic type, striae rubrae and other aspects of striae distensae. Such presentations of dermal atrophy possibly induce subcutaneous fat herniations, and easy bruising. Among our 131 EDSH women, 88(67.2%) exhibited scars, corresponding to 65 (49.6%) enlarged atrophic scars, 21(16.0%) had normal scars and 2(1.5%) showed hypertrophic ones. Nevertheless, delayed wound healing status was disclosed in only 19(14.5%) women. Delayed wound healing and atrophic enlarged scars are clues for EDSH, particularly in esthetic surgery. Indeed, in EDSH patients, less robust tissues, with increased blood vessel fragility and delayed wound healing commonly lead to complications set in some surgical interventions.[23,24]

DERMAL ULTRASTRUCTURAL ABNORMALITIES

The EDSH diagnosis appears frequently missed following the casual clinical presentation. In fact, joint laxity commonly decreases with age and/or following some degenerative processes. In addition, and each single joint is not considered in the Beighton score. Tenascin-X deficiency is present in some EDSH,[24,25] but the genetic mutations remain undisclosed in the majority of the EDSH cases.

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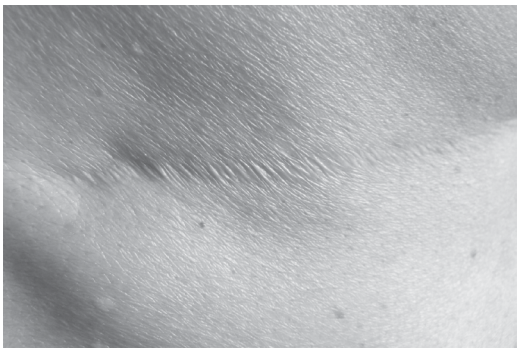

Figure 1: Atrophic scar in EDSH.

Skin ultrastructural abnormalities still represent an important aid for the EDSH diagnosis.[19,21,26-32] Each ultrastructural dermal changes, although individually unspecific appeared relevant and contributed to the diagnosis. Ultrastructural examinations revealed collagen and elastic fiber changes that were more obvious in the reticular dermis. The collagen scaffolding was altered showing bundles with uneven fibril sizes. Some fibril outlines were discretely serrated, and others showed flower-like transversal sections. Some fibrils appeared whirled and the interfibrillar spaces were unevenly enlarged (Figure 2). Elastic fibers exhibited irregular contours. The combination of such aspects was absent in skin samples from normal individuals. In short, ultrastructural changes were not only focused on flower-like collagen fibrils, but rather on the erratic orientation of the collagen fibrils, and their irregular interfibrillar spacing,[29,31] as well as on abnormal elastic fibers, granulo-filamentous deposits and large stellate hyaluronic acid-like globules.[30-31] Some of these non-fibrillar deposits combined with thinned collagen fibrils were possibly related to alterations of tenascin-X.[24,25]

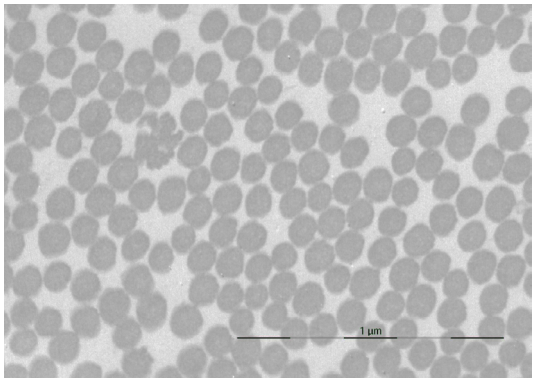

Figure 2: Flower-like collagen fibres and uneven interfibre spacing.

SPONTANEOUS CERVICAL ARTERY DISSECTION

The dermal ultrastructure of EDSH shows some similarities with the aspect present in some cases of the condition called Spontaneous Cervical Artery Dissection (SCAD).[30-34] The clinical criteria are, however, distinct. These two conditions have been reported in the same family.

CONCLUSION

The EDSH is a multisystemic disorder with multiple implications in the quality of life (QoL). It is mostly diagnosed in women. Some minor cutaneous signs, such as hyperextensibility, velvety skin, striae distentae and atrophic scars should evoke the EDSH diagnosis. A skin punch biopsy with ultrastructural examination is currently helpful to confirm the diagnosis and for adequate management. Currative and plastic surgeons should be aware of this pathology for limiting postsurgical complications and unaesthetic scars. Peculiar surgical approaches are recommended for EDSH patients.[35,36]

The fibrous collagen structure and its environment are uncovered by electron microscopy. In spite of the relatively unspecific ultrastructural criteria of EDS, the global architecture and the ultrastructure of the dermis are of diagnostic relevance, and they occasionally suggest a specific EDS type.[37] The defects in collagen fibril formation are likely multiple suggesting variable penetrance. Abundant granulofilamentous deposits are found in subjects with mutations in the gene coding for tenascin-X.

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CONFLICTS OF INTEREST: None.

CONSENT STATEMENT

All participants agreed to publish the manuscript, entitled "*Clinical and ultrastructural skin alterations in the Ehlers-Danlos syndrome, hypermobility type*" in Dermatology - Open Journal, and provided the written informed consent.

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