



Gynecologic and obstetric impact of the Ehlers-Danlos syndrome : clues from scrutinizing dermal ultrastructural alterations

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Abstract

Background: The Ehlers-Danlos syndrome (EDS) represents a heterogeneous group of heritable connective tissue disorders chiefly characterized by joint laxity, increased skin distensibility and connective tissue fragility. Each EDS type corresponds to a multisystemic disorder with widespread implications. Physicians evoke the EDS diagnosis in presence of some typical cutaneous signs, such as atrophic scars and frequent hematomas.

Methods: To revisit the transmission electron microscopy support from skin biopsies when screening EDS in gynecology-obstetrics.

Results: EDS women commonly suffer from a series of gynecologic and obstetric disorders. Dermal ultrastructural changes are keynote features suggesting some EDS types.

Conclusion: Gene mutations are mostly identified in the classic and vascular EDS types, but only in sporadic cases of the hypermobile EDS type which apparently represents the most frequent type. Dermal ultrastructural changes represent relevant diagnostic clues for the practitioner. Preconception counseling about possible complications is welcome. Management requires precise diagnosis of the EDS type.

Keywords: Ehlers-Danlos syndrome, gynecology-obstetric disorders, dermal ultrastructure, transmission electron microscopy

Introduction

Ehlers-Danlos syndrome (EDS) represents a heterogeneous group of heritable connective tissue (CT) disorders clinically characterized by variable combinations of increased skin distensibility and elasticity, joint laxity and CT fragility. The fibrillar collagen and the elastic fibres are altered in the dermis, ligaments, vessel walls and internal organs. Thus, the risk of some specific gynecologic and obstetric alterations is higher in EDS women than in EDS-unaffected ones. The combination of clinical assessments and family history probably discloses only a minority of EDS patients. Measurements of the mechanical properties of skin [1-3] and dermal histopathology disclose more EDS subjects with moderate skin changes exhibiting or not degenerative joint alterations.

The aim of the present review is to revisit the implication of EDS in some gynecologic and obstetric conditions.

Ehlers-Danlos syndrome classification

Six distinct EDS types are recognized according to clinical features, specific underlying genetic and biochemical defects, and patterns of inheritance [4]. They correspond to the classic, hypermobile, vascular, kyphoscoliosis, arthrochalasia, and dermatosparaxis types. However, some cases remain unclassified. The two most frequent conditions are the classic and hypermobile types, respectively. Major and minor

characteristics are recognized in the different EDS types.

In EDS classic type, mutations are often disclosed in the COL5 gene [5,6]. The COL3 gene is commonly disturbed in the EDS vascular type [7]. Sporadic mutations, such as TNXB haploinsufficiency, were reported in hypermobile EDS, although mutations remain undisclosed in the majority of cases [8].

Joint hypermobility is present at variable extent in any EDS type. It is conveniently assessed according the Beighton scale. A score reaching 5/9 or above defines EDS [4]. However, this score interpretation is sometimes uncertain. In fact, many women and children, as well as some ethnic groups such as Asian people exhibit more joint laxity [9-11]. In addition, every joints are not scrutinized for establishing the Beighton score. Furthermore, joint hypermobility becomes commonly less evident with aging as a result of pain, traumas and surgical procedures.

Increased skin distensibility is another major diagnostic criterion for the EDS classic type. It is assessed by pulling up the skin on the volar aspect of the forearm until resistance is felt. Atrophic papyraceous scars, molluscoid pseudo-tumors, violaceous scar hyperpigmentation and easy bruising are common. Hypertrophic scars are occasionally observed in EDS classic type [6]. Spheroids correspond to small, hard, freely moveable nodules present in the subcutaneous tissue. They correspond to fibrous and calcified fat lobules.

The EDS hypermobile type is considered as the least severe and the most frequent type. Hypermobile EDS appears commonly underdiagnosed [6,12]. It exhibits minimal skin changes. Skin appears velvety and discretely hyperextensible. Scars are commonly atrophic although do not look papyraceous. Striae distensae and pyezogenic papules are present in EDS classic and hypermobile types [6,12]. Absence of the lingual or inferior labial frenulum was recently reported in EDS hypermobile type [13,14]. Borderline EDS patients are diagnosed when minor signs and family history are present. Accordingly, some authors consider the family benign joint hypermobile syndrome as a mild form of EDS hypermobile type [12,15].

The EDS vascular type [7] is characterized by translucent, but not overextensible skin, associated with atrophic scars, repeat ecchymoses, increased risk of pneumothorax and spontaneous organ and vascular ruptures. Hands and feet exhibit acrogeria appearance.

Other EDS types represent more rare conditions. Hypotonia, early onset scoliosis and risk of ocular rupture are found in kyphoscoliotic EDS. Skin is mildly overextensible, and scars are moderately widened. In this EDS type, arterial rupture is a major cause of fatal issue. EDS arthrochalasia patients suffer from congenital hip dislocations and increased risk of fractures. Laxity, doughy skin, poor wound healing and typical facies are major signs of human dermatosparaxis. The rare periodontitis variant of EDS associates classic EDS features, periodontitis, complete early loss of adult dentition and leg ulcers [16].

EDS-associated gynecologic disorders

Irregular menses, metrorrhagias, severe dysmenorrhea, dyspareunia, vulvodynia and vaginal dryness are frequent in EDS women [12,17-19]. Chronic pains represent the most common neurologic complaints [20]. They are commonly associated with joint hyperlaxity and dislocation. Involvement of the S2-S4 joints is responsible for the Alcock canal syndrome with pelvic pain worsened by sitting [21].

Recurrent preterm premature rupture of fetal membranes

Preterm premature rupture of fetal membranes (PPROM) is defined when the event occurs before the onset of labor and occurs before 37 weeks of gestation. The etiology is multifactorial, including infections, tobacco smoking and poor socio-economic factors [22,23].

In pregnancy, the membranes surrounding the amniotic cavity correspond to the amnion and chorion. The amnion is composed of 5 layers including a compact CT sheet mainly composed of type I and III collagen fibrils. PPRM is associated with a reduction in amnion collagen content [24], probably related to disturbance in collagen metabolism [25]. Hence, CT disorders such as EDS possibly alter the fetal membranes inducing PPRM and miscarriages. This hypothesis is supported by the increased incidence of preterm delivery and

late abortions in EDS patients [17,19,26,27]. This incidence is higher when the fetus is affected [27].

Some apparently healthy women present recurrent PPRM. In these cases, an underlying CT disorder may be suspected. Such hypothesis is supported by the presence of EDS-like dermal abnormalities in some women who present recurrent PPRM without showing any obvious clinical evidence for an already defined EDS [28].

Pregnancy and post-partum complications

Severe back and pelvic pains, and bleeding are the most frequent complains in EDS [17,19,27]. Major post-partum complications are seen in EDS vascular, kyphoscoliotic types, such as intestinal and vascular ruptures [17,27,29-31]. Outcome of pregnancy is often unaffected in EDS hypermobile type [17,27,32]. Nevertheless, some complications are reported including abnormal fetal presentations, increased rate of suture dehiscence and delayed wound healing, uterus atonia, hemorrhage, pelvic prolapse, deep venous thrombosis and coccyx dislocation [17,19,27,32,33]. Pelvic prolapse may occur in nullipara [34].

Diagnosis

EDS should be suspected in presence of abnormal scars and ecchymoses. The diagnosis and classification of EDS is mainly based on clinical signs.

Increased skin distensibility defines the ability of the skin to be stretched beyond normal limits and rapidly returning to its original position. It is mostly important in classical EDS type. Several methods are available for assessing any abnormal skin tensile properties [1-3].

The Beighton score for joint hyperlaxity should be assessed, and personal history must be taken in consideration, such as preterm birth, hip or shoulder congenital dislocations. Familial history is particularly helpful. Some patients do not meet the current EDS criteria. A further set of diagnostic criteria, including common features such as functional bowel disorder, cardiovascular dysautonomia, has been proposed [35], but it is not yet validated. The revision of the EDS nosology is required [36], for unifying available diagnostic criteria.

Gene mutations are presently not yet found in every EDS case, probably because technical limitations in sequencing methods. There is not yet clear phenotype-genotype correlations. Indeed, in the majority of cases of EDS classical type collagen V mutations are identified although other collagen I mutations [37] as well as tenascin-X deficits are reported [38,39]. The latter alteration is further responsible for EDS hypermobile type [5]. Therefore, other investigations should be performed to confirm the precise diagnosis of EDS. Histopathological dermal changes with reduction or absence of Factor XIII a+ dermal dendrocytes type1 (DD1) are observed in the EDS classic type [40] and in dermatosparaxis [41]. In EDS, there are no type-specific ultrastructural alterations in collagen and elastic fibers, except for the hieroglyphic-shaped

fibril cross-sections of the EDS dermatosparaxis type [41]. In spite of heterogeneity in both the structural and biochemical abnormalities, the overall architecture and ultrastructure of the dermal components changes are of diagnostic relevance and they occasionally suggest the EDS type [42-45]. Furthermore, they contribute rapidly to the diagnosis before getting the information from genetic analysis. Ultrastructural abnormalities are most pronounced in the reticular dermis and focused on collagen fibrils under the aspect of flower-like, unraveled, serrated, twisted and hieroglyphic fibrils. In EDS classical type, the flower-like collagen fibrils (Figure 1) are rare and dispersed among round-section fibrils. Their size is markedly altered and their morphometric aspect suggests an uncontrolled fibrillogenesis [46]. In the EDS hypermobile type, the size of the flower-like collagen fibrils is smaller. The collagen fibrils are commonly misoriented [47]. In most of EDS hypermobile type cases, other dermal components exhibit changes such as abnormal elastic fibers, granulo-filamentous deposits and presence of large stellate hyaluronic acid-like globules [48]. In the EDS vascular type, the dermis is thinned to about one third. The collagen bundles and the other dermal components are loosely arranged. Both the collagen bundles and their fibrils are thin. Composite, notched or hieroglyphic fibrils are absent. The elastic fibers appear branched or fragmented and seem increased in numbers. Fibroblasts exhibit dilated endoplasmic reticulum filled with a granular material.

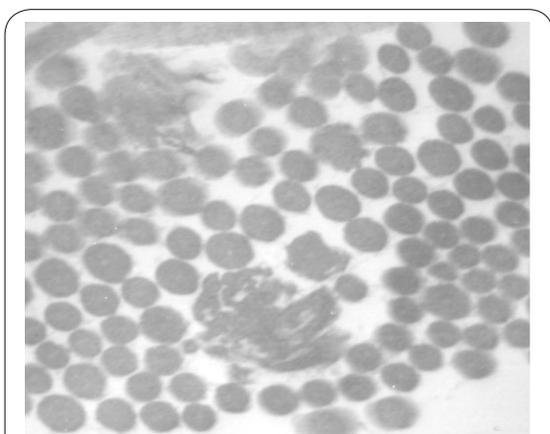


Figure 1. EDS classic type: flower-like collagen fibrils, variable diameter collagen fibrils and irregular interfibrillar spaces (16,500x).

Management

Understanding EDS types and their complications constitutes an important aid for familial counseling and management of pains and pregnancy in EDS patients.

Vulvodynia contributes to sexual dysfunction and chronic pains alter the quality of life. It is important for these patients and their relatives to know that pains have not a psychosomatic origin. Anxiety is commonly observed, because the

misunderstanding of their pains.

Prenatal counseling is vital in EDS vascular and kyphoscoliotic types, as well as some classical type with the risk of arterial rupture [49,50], because they represent important complications and life risks. There is no consensus in the literature about the timing and mode of delivery for pregnant vascular EDS women. Conversely, there is a lack or only benign complications in EDS hypermobile type. However, the diagnosis must be established before pregnancy in order to elaborate specific management procedures and reduce post-partum complications. Some authors prefer cesarean section to minimize the risk of pelvic prolapse [2]. Because of abnormalities in wound healing, waiting time before suture stitches removal after cesarean or episiotomy may be doubled.

Prophylactic measures may be taken for reducing the risk of cardiovascular dysautonomia in general anesthesia or cerebrospinal fluid leakage in peridural anesthesia.

Conclusions

There are numerous gynecologic and obstetric implications in EDS. Physicians should be aware of the clinical signs of this syndrome. Some cutaneous signs, such as skin hyperextensibility, velvety or translucent skin, atrophic scars, should evoke the EDS diagnosis. The diagnosis and the classification of EDS are essentially rooted on the clinical presentation. They are confirmed by dermal ultrastructural observations and, in some cases, particularly in the classical and vascular types by the identification of specific genetic mutations. Knowledge of the EDS types is important for reproductive counseling and pregnancy management. It is advisable to get a preconceptional diagnosis for facilitating the management of these patients.

Obstetric guidelines are not established for EDS patients. The management should be made case by case, in function of the EDS severity. In EDS classical and hypermobile type, maternal and fetal outcomes are generally good, but maternal complications related to the abnormal CT, occur more often than in the general population. EDS vascular and kyphoscoliotic types, as well as some cases of the classical type, are occasionally associated with severe maternal morbidity and even mortality.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	THL	GEP	CPF	PD
Research concept and design	✓	--	--	--
Collection and/or assembly of data	✓	--	--	--
Data analysis and interpretation	✓	✓	✓	✓
Writing the article	✓	✓	--	--
Critical revision of the article	✓	✓	✓	✓
Final approval of article	✓	✓	✓	✓
Statistical analysis	--	--	--	--

Acknowledgement

The authors appreciate the excellent secretarial assistance of Mrs. Ida Leclercq.

Publication history

Editor: Ingrid Kowalcek, University Schleswig Holstein, Germany.

Received: 17-Feb-2014 Final Revised: 17-Mar-2014

Accepted: 20-Mar-2014 Published: 26-Mar-2014

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Citation:

Hermanns-Lê T, Piérard GE, Piérard-Franchimont C and Delvenne P. **Gynecologic and obstetric impact of the ehlers-danlos syndrome : clues from scrutinizing dermal ultrastructural alterations.** *Gynecol.* 2014; **2**:1. <http://dx.doi.org/10.7243/2052-6210-2-1>