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Case Report

Classical type Ehlers–Danlos syndrome with autosomal dominant tubulointerstitial kidney disease, from a dermatological standpoint

Walaa Fadhil Abbas, Tamrazova Olga Borisovna*, Molochkov Anton Vladimirovich, Kolbe Olga Borisovna[#], Bekmurzaeva G.B[##], Stadnikova Antonina Sergeevna***

Department of Dermatovenerology with course Cosmetology, RUDN University, Moscow, Russia.
* Federal State Autonomous Educational Institution of Higher Education "Peoples' Friendship University of Russia" of the Ministry of Education and Science of the Russian Federation; Children's City Clinical Hospital named after PER. Bashlyaeva, Moscow Department of Health, Russia.
** Moscow Regional Clinical Research Institute named after M.F. Vladimirsky (MONIKI), Russia.
[#] Department of Propaedeutics of Children's Diseases of the Russian National Research Medical University. N.I. Pirogov of the Ministry of Health of Russia.
[##] Department of Nephrology of the Children's City Clinical Hospital named after Z.A. Bashlyaeva, Moscow City Health Department.

Abstract

Ehlers–Danlos syndrome (EDS) is a group of non-inflammatory hereditary connective tissue diseases that impair collagen and elastin metabolism, resulting in collagen defects and/ or disordered deposition in tissues, and can cause a variety of multisystemic symptoms. It has a wide range of genetic origins, molecular abnormalities, and connective tissue ultrastructure (CT). EDS is caused by changes in over 19 genes that are present at birth. The kind of EDS is determined by the gene that is impacted. EDS has been divided into 13 subtypes, with a fourteenth variant reported in 2018. One of the most prevalent manifestations is the hypermobile version (EDSH). Hippocrates first described EDS in the 4th century B.C. The syndromes are named after two physicians who described them around the start of the twentieth century: Edvard Ehlers and Henri-Alexandre Danlos. The altered mechanical functions of the involved tissues cause a variety of cutaneous (hyper elasticity, fragility, and atrophy), rheumatological (joint laxity and hypermobility), and vascular (vessel wall fragility and easy bruise) changes. The diagnosis is usually made using a combination of clinical criteria, skin biopsies, and genetic studies. EDS is normally diagnosed at birth or in early childhood, but symptoms can sometimes appear in adolescence or young adulthood. Some gynecologic and obstetric problems are frequent among women. When a patient is identified, a thorough examination of all family members is required. Aortic dissection and joint dislocations are two major complications that can occur.

Key words
Ehlers–Danlos syndrome, hereditary connective tissue diseases, skin hyper elasticity.

Introduction

Ehlers-Danlos syndrome (EDS) is a rare multisystemic connective tissue disorder that affects one in every 5000 people, with worldwide distribution as no racial predisposition has been identified. EDS is caused by changes in over 19 genes that are present at birth. The kind of EDS is determined by the gene that is impacted. Autosomal dominant inheritance is the most common, but autosomal recessive and X-linked recessive

Address for correspondence
Dr. Walaa Fadhil Abbas
38-Й Юго-Запада Кварт.,
К1, 1КОР, Moskva, Moscow Oblast,
119421, Russia.
Ph: +79875396330
Email: walaafadil1@gmail.com

types have also been found.[1] It can also be associated with an individual's (sporadic) DNA mutation. Despite the fact that the female to male ratio of the genetics clinic's general patient group is 1:1 (50.1% female, 49.9% male), the Ehlers-Danlos Syndrome hypermobility type (HEDS) patients identified by this clinic were mostly female (78.3% female, 21.7% male).[2] It was initially defined as a condition of hyper elasticity of the skin where the patient is prone to severe bruising by the Danish dermatologist Edvard Ehlers in 1901. In 1908, Henri Alexander Danlos, a French dermatologist, noticed the unusual cigarette paper like scars and reported on molluscoid or fibrous pseudo tumors as part of the disease. In 1934, Pomeau-Delille and Soulie called the disorder Ehlers-Danlos syndrome.[3] It is underdiagnosed because of the variability of clinical expression among individuals, even within families. Specific mutations in the genes coding for collagen types I, III, and V, as well as genes encoding enzymes involved in collagen production and processing, are thought to cause Ehlers-Danlos syndrome.[4] All other forms of tissue in the body are supported by connective tissue, which unites or divides them. It is made up of cells that are surrounded by a fluid compartment termed the extracellular matrix (ECM). Collagen and elastin fibers are proteins produced by fibroblasts and comprise the major backdrop of connective tissues, along with reticular fibers and other ground components. situated throughout the majority of the body's organs (skin, blood vessels, bones, heart, lungs, kidney, gastrointestinal tract, and urogenital tract). Failure to properly produce these important proteins will cause a range of structural and functional abnormalities in these organs. Under the current 2017 classification system,[5] 13 types of EDS are identified, many of which are linked to mutations in at least 20 different genes. The majority of these kinds are marked by joint hypermobility - often known as "loose" joints, which stretch beyond their normal range and risk dislocation - and delicate, fragile skin that is readily torn and scarred. Symptoms of EDS can range from moderate to life-threatening, depending on the kind. A novel autosomal recessive variety of Ehlers-Danlos syndrome has been discovered; it is extremely rare, having only been diagnosed in four people from three different families thus far.[6] It is caused by unique polymorphisms in the AEBP1 gene and carries the same spectrum of presentations as other types of EDS.[6] One of the rare skin findings in EDS is piezogenic pedal papules. These papules are compressible, yellowish or skin-colored, usually appear on the plantar aspect of the foot and heel, and are more marked on the medial aspect that represents herniations of subcutaneous fat through the reticular dermis.[7] Livedo reticularis and elastosis perforans serpiginosa (EPS) are two further clinical symptoms of EDS. EPS is most commonly seen in vascular EDS (vEDS), although it has also been seen in Hypermobile EDS.[8]

Case report

A 14-year-old female with a complex past medical and family history presented to the Department of Nephrology of the ZA Bashlyaeva Children's Clinical Hospital in Moscow complaining of chronic recurrent pain in the lumbar region. associated signs and symptoms: gastritis, reflux, urinary incontinence and heavy menstruation. She was a little anxious and afebrile. Her vital indicators were all within normal limits. Heart sounds were loud, there were no murmurs. On physical examination, the abdomen was soft but diffusely tender. The liver, spleen, and lymph nodes were not enlarged. Severe peripheral edema was noticed. Her developmental parameters were: (height of 162 cm, weight of 45 kg). There were no deformities of the bones, joints, or posture

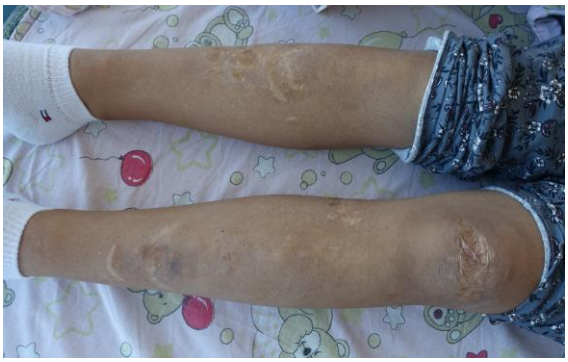

Figure 1 on the left knee, atrophic thin skin with wrinkled tissue like paper surface, atrophic scars and hemosiderin hyperpigmentation due to old bruises . similar changes visible on both legs.

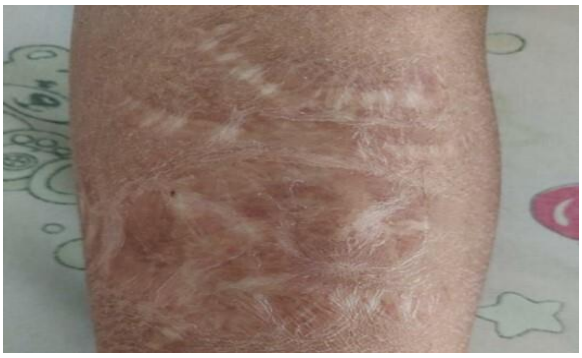

Figure 2 stellate like atrophic linear scars with un defined orientation on the left forearm.

disorders. Laboratory tests, including blood and urine tests, were without pathology. The indicators of creatinine, urea and uric acid were within the normal limit. The coagulation profile was normal. Nephrotic syndrome was diagnosed according to laboratory investigations (diuresis of 800 ml per day, hypoproteinemia of 45 g/l, hypoalbuminemia 19 g/l, hyperlipidemia cholesterol 9.8 mmol/l, proteinuria up to 5 g/l, hematuria from 40 erythrocytes per field of view, and daily protein loss of 2.5 g) and ultrasound findings. An echo of the heart revealed transverse trabeculae, ectopic chords in the left ventricle. Diffuse interesting skin changes were noticed by examiners and dermatological consultation was done. Physical examination of the skin revealed soft, fragile, velvety smooth, hyperextensible, easily bruised skin with diffuse hyperpigmentation and linear atrophic scars without specific orientation, mainly on the thighs, legs, left knee **(Figure 1)** and forearm **(Figure 2)**. The skin appendages were also affected, as loss of villus hair and hypohidrosis were noticed, in addition to thin, sparse scalp hair and slightly dystrophic nails. oral mucosa, teeth, and genitalia without specific changes. The serological markers of systemic diseases (C3 and C4 complement, anti-cardiolipin, anti-dsDNA, anti-pANCA/AT to MPO, anti-cANCA/AT to PR3, anti-2-glycoprotein, and lupus anticoagulant antibodies) were all within normal limits. Viral serology was negative. Regarding her past history, she was born at 35 weeks due to an early rupture of amniotic fluid, with an Apgar score of 8/9, a weight of 2250 g, and a length of 48 cm. The child was transferred to the ICU. There was bleeding in the area of the left eyelid or eye (hemolacria?) with the development of anemia (Hb 68 g/l). The therapy was carried out with erythrocyte transfusion. She has had chronic recurrent left-sided otitis for 2 years. Vaccinations were done according to an individual schedule. The skin was abnormally thin, fragile, and wrinkled like tissue paper. According to the parents' words, with the slightest injury, the skin was damaged, resulting in extensive scars in the future. Her family history: her mother and brother had nephropathy; her father also had an increased vulnerability of the skin with scarring. Her grandmother, from her mother's side, had hypertension; her uncle suffered from enuresis until the age of 10; he died in an accident. Her grandmother, on her father's side, died at 73 from bowel cancer. Kidney and skin biopsy with immunofluorescence assay were performed because of atypical nephrotic syndrome (late onset and steroid resistance) and unusual skin changes. Renal biopsy exhibits Focal segmental glomerulosclerosis and skin biopsy revealed dermal and epidermal atrophy with impaired distribution and structure of collagen fibers and destruction of elastic fibers with irregularities in

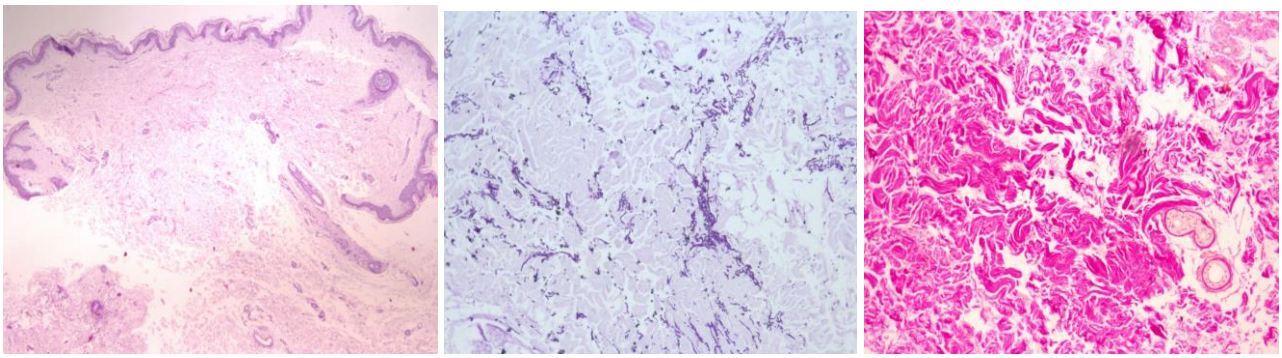

Figure 3 Histological images of the skin of a classical Ehlers–Danlos syndrome (EDS) patient (A): Light microscopy of hematoxylin-eosin stained sections of skin showed an epidermis with a slightly altered contour and atrophy. Irregular collagen and elastin bundles of various sizes with wide areas of destruction were observed in the middle and reticular dermis. (B): Weigert's elastic staining shows ultra-structural abnormalities of elastic fibers of the dermis which appear coarse, clumped, disoriented, and fragmented. (C): Van Gieson's staining shows the disorganized appearance of loosely dispersed collagen fibers in a non-parallel arrangement with various sizes and shapes.

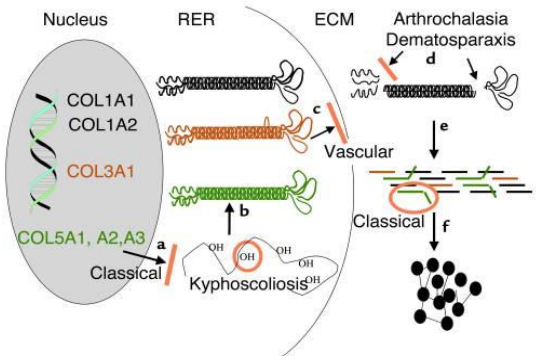

Figure 4 The biosynthesis process for fibrillar collagens expressed in skin, including identification of stages that are impaired in various kinds of EDS.

size and orientation **(Figure 3)**. Electron microscopy revealed defects in the striations of the collagen fibers. The results of the complete sequencing of the exome were obtained. Two mutations were identified: 1. in the UMOD gene (heterozygous state), pathogenic for the development of autosomal dominant tubulointerstitial kidney disease; and 2. a mutation was found in the COL5A1 gene in exon 1. Taking into account the patient's history, the results of histological examination of the skin, the familial nature of skin lesions, and the identified mutation, Ehlers-Danlos syndrome type 1 was diagnosed. Medical genetic counseling of the patient's family was recommended. The treatment of the patient was mainly supportive therapy with symptomatic treatment with steroid sparing agents, cyclosporine A (CsA) at a dose of 200 mg (4 mg/kg) for 6 months, antihypertensive nifedipine (12.5 mg), vitamin D 1500 IU/day, albumin (25%) at 0.5 g/kg twice daily over 2 to 3 h, followed by IV furosemide at 1 mg/kg per dose, and omega 3 antioxidants.

Discussion

Ehlers-Danlos syndrome is one of the rare genetic disorders that is underdiagnosed in general medical clinics, with delayed diagnosis until adolescence being the usual picture. This may not be a big problem for some types, like classical and hypermobility forms, which have a normal life expectancy. But if a statistic for a dermatological diagnostic impact factor existed, vascular Ehlers-Danlos syndrome (vEDS) would be at the top. Frequently undetected until a disaster occurs like aneurisms, rupture, or dissections of major vessels.[9] The idea that EDS is a condition of fibrillar collagen metabolism is backed up by the discovery of unique abnormalities in the collagen biosynthetic pathway that result in clinically different EDS forms **(Figure 4)**.[10] This will lead to defective collagen and elastin in the dermis connective tissue, which will also affect the formation of skin appendages, including hair follicles, sweat,

and sebaceous glands.[11] To our knowledge, this is the first case of EDS classical type associated with autosomal dominant tubulointerstitial kidney disease (ADTKD) reported in the literature. There is a reported association of EDS with autosomal recessive interstitial nephritis.[12] In general, urogenital system changes associated with EDS are reported as: renal vascular infarction in the vascular type,[13] reflux nephropathy, hypoplastic anomalies, cystic diseases, tubular acidosis, stress incontinence, and bladder diverticuli.[14] Skin hyper extensibility with atrophic scarring and widespread joint hypermobility are the current primary criteria for classical type EDS. Others mucocutaneous symptoms (easy bruising, soft, doughy skin, skin fragility, molluscoid pseudotumor, subcutaneous spheroids and hernia), epicanthal folds, joint hypermobility problems, and an afflicted first-degree relative are minor factors. Major criterion 1 plus either major criterion 2 or 3 minor criteria are the minimal criteria that warrant molecular testing.[15]

The clinical picture may also include several organ systems such as gastrointestinal, cardiovascular, uro-gynecological, and neuropsychiatric. Women with EDS are more likely to experience dysmenorrhea, irregular menses, metrorrhagias, and dyspareunia.[15] There is a great overlap in clinical and systemic findings between various forms of EDS, so genetic testing is mandatory to confirm the diagnosis of a particular type. The classical type is related genetically to nail patella syndrome (a genetic autosomal dominant disease causing dystrophic nails and hypoplastic patella).[16] The patient in this case report met the diagnostic criteria of classical EDS as she had one major (skin hyper extensibility with atrophic scars) and three minors: skin fragility, easy bruising, and similar findings in first-degree relatives (her father). In addition to the other systemic organic affections (renal, cardiac, and gynecological) that were mentioned in the case presentation, there is also a genetic mutation in the COL5A1 gene that confirms the diagnosis. Preterm rupture of the membranes and prematurity can occur when the mother is affected and also when the fetus is affected,[17] as in this case. There is no cure for EDS and the treatment focuses mainly on physical therapy, occupational therapy, protective wear, ascorbic acid supplementation (2 g/day), avoiding excessive sun exposure to reduce the risk of premature skin aging, and Vasopressin to normalize bleeding time. Although bleeding is related to capillary fragility rather than a clotting disorder, Vasopressin can help in the case of bruising or epistaxis.[18] The differential diagnosis of EDS includes Marfan's syndrome, generalized familial joint hypermobility syndrome, cutis laxa, pseudoxanthoma elasticum, osteogenesis imperfecta, Loeys-Dietz syndrome, Larsen's syndrome, and other congenital connective tissue diseases.[19]

Conclusion

We can consider the skin (the largest organ in the body) as a mirror that reflects many genetic disorders of connective tissue, as skin changes can be the only visible findings that may be associated with serious hidden systemic changes. And that is because of the structural alterations due to genetic mutations that affect collagen, elastin, glycoproteins, and proteoglycans (the matrix of the dermis) and their interactions with other structures (epidermal appendages, nerve and vascular networks), which ultimately lead to unusual and unique changes that may be seen early in life. Astute dermatologists who investigate a syndromic disorder diagnosis based on these early atypical skin changes may save a patient's life before an acute danger event occurs, which can happen in some kinds of EDS.

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