I. GENETICS

CLINIC AND GENETIC HETEROGENEITY IN EHLERS-DANLOS SYNDROME

Maria Puiu[1], Liliana Vasile[1]
[1]University of Medicine and Pharmacy "Victor Babes" Timisoara, Romania

Abstract

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of hereditable connective tissue disorders characterized by articular hypermobility, skin hyperextensibility, and tissue fragility. EDS type IV being the most life-threatening form. It is characterized by a type III collagen deficiency and this disease involves a col3A1 gene mutation (5, 6). We report the case of a 47 year-old woman with type IV EDS. Each of her two children presented clinical elements of EDS: her daughter (25 years old) and her son (18 years old). Clinic and genetic heterogeneity of the disease is very evident in this family, the three family members presenting clinical symptoms and comorbidities which made difficult the attempt to integrate them in a certain EDS type; these three cases presented a various clinical expression and severity. Another particularity is also represented by the presence and high frequency of associated spontaneous bone fractures.

Key word: Ehlers-Danlos syndrome, genetic heterogeneity, gene COL3A1.

Background

Ehlers-Danlos syndrome (EDS) refers to a group of disorders linked by genetic defects that affect collagen structure and function. Collagen is a major protein in the body and forms the base foundation for connective tissues. Owing to a genetic defect in collagen manufacture, tissues affected are abnormally weak, depending on the specific genetic defect. Major symptoms can include skin fragility, excessive skin stretchability, and excessively loose joints. Some types of EDS are characterized by fragile blood vessels or abnormal spine curvature (3).

Collagen is a strong, fibrous protein that lends strength and elasticity to connective tissues such as the skin, tendons, organ walls, cartilage, and blood vessels. Each of these connective tissues requires collagen tailored to meet its specific purposes. The many roles of collagen are reflected in the number of genes dedicated to its production. There are at least 28 genes in humans that encode 16 different types of collagen. Defects in these genes can affect basic construction as well as the fine-tuned processing of the collagen (7).

According to the Ehlers-Danlos National Foundation, 1 in 5,000 to 1 in 10,000 people are affected by some form of EDS. EDS is an inherited disease, and its pattern depends on the affected gene (1). There are three types of inherited patterns: autosomal dominant, autosomal recessive, and X-linked (extremely rare).

Up until 1997, the types of Ehlers-Danlos Syndrome were classed from numbers I-XI. However, after the New Nosology was released in 1997, the types were described under different names, eg. Classical type EDS (formerly types I and II), or Hypermobility type EDS (formerly type III). It is generally thought that one can only have on type of EDS, but more and more people are manifesting more than one type at the same time, challenging this logic.

The new classification is simpler and based more on descriptions of the actual symptoms. EDS is now classified into six major types: classical, hypermobility, vascular, kyphoscoliosis, arthrochalasia, and dermatosparaxis, and a collection of rare or poorly defined varieties (4).

Formerly called EDS type IV, EDS vascular type carries the risk of premature death. The connective tissue in the intestines, arteries, and uterus is unusually weak, leading to a strong possibility of organ or blood vessel rupture. Such ruptures are more likely between ages 20–40, although they can occur any time, and can be life-threatening. The large joints have normal stability, but small joints in the hands and feet are loose. The skin is thin and translucent, with veins dramatically visible. The skin bruises easily. Other complications can include collapsed lungs, premature aging of the skin on the hands and feet, formation of openings between arteries and veins, and complications following surgery. EDS vascular type is inherited in an autosomal dominant manner (2).

Case report

We report the case of a 47 year-old woman with type IV EDS.

Familial history: The parents are not consanguineous first cousins. Her father had a clinical features of EDS, also, the grandfather and two brothers showed varying degrees of joint and skin hyperextensibility (fig. 1).

The medical history of our patient included multiple spontaneous bone fractures, anomalies of

subclavian artery (fig. 3, 4), moderate bruising and rupture of hollow organs such as the intestine and stomach, requiring repeated surgical interventions, generalized joint hypermobility (fig. 2), skin hyperextensibility, chronic joint pain, recurrent joint dislocations, extensive bruising, characteristic facial appearance, varicose veins, progressive scoliosis, osteopenia. Each of her two children presented clinical elements of EDS: her daughter (25 years old) presented especially molluscoid pseudotumours, these are firm, fibrous lumps measuring up to 2 - 3 cm which develop over pressure points such as the elbows and knees, subcutaneous spheroids. Approximately one third of affected individuals describe small, firm nodules like 'ball-bearings' just beneath the skin. These consist of fibrotic and calcified fat which overlay bony areas such as the shins, (skin biopsy, fig. 5-6-7), joint hypermobility, chronic joint pain with recurrent joint dislocations, easy bruising and spontaneous bone fractures. Her son (18 years old) presented recurrent joint dislocations, moderate skin hyperextensibilty, articular hypermobility and autism.

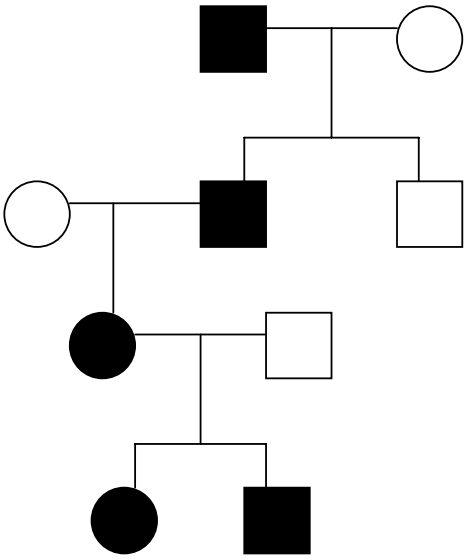

Fig. 1. Pedigree chart of a 47 year-old woman with type IV EDS.

Fig. 2. Generalized joint hypermobility.

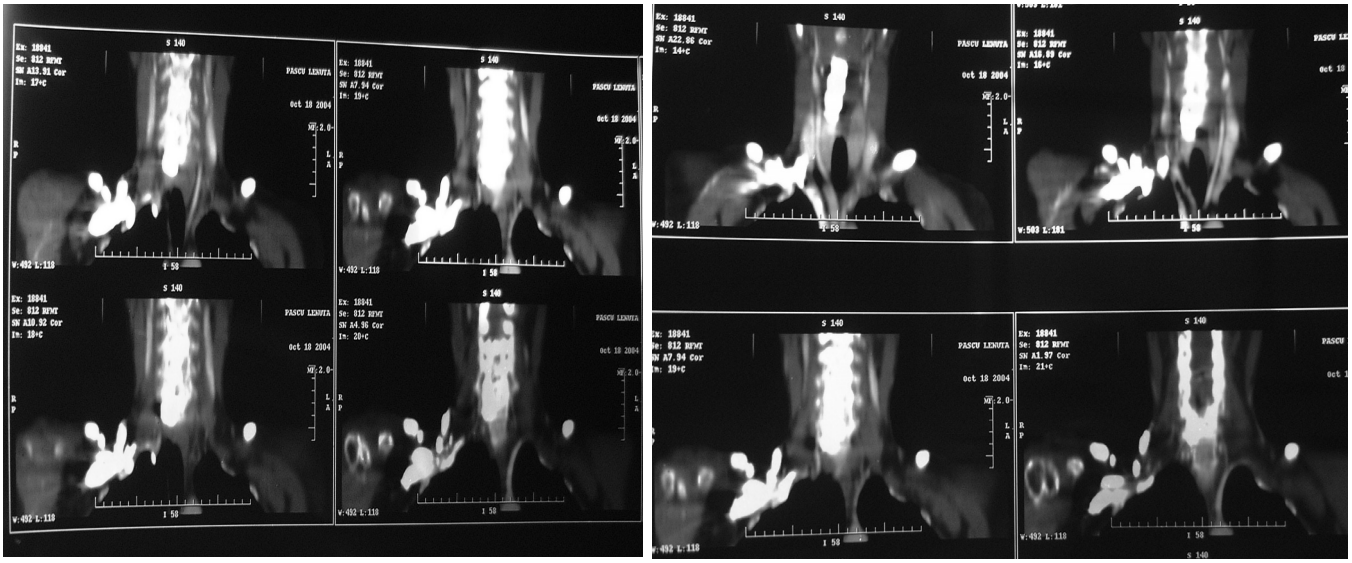

Fig. 3-4. MRI: Anomalies of subclavian artery

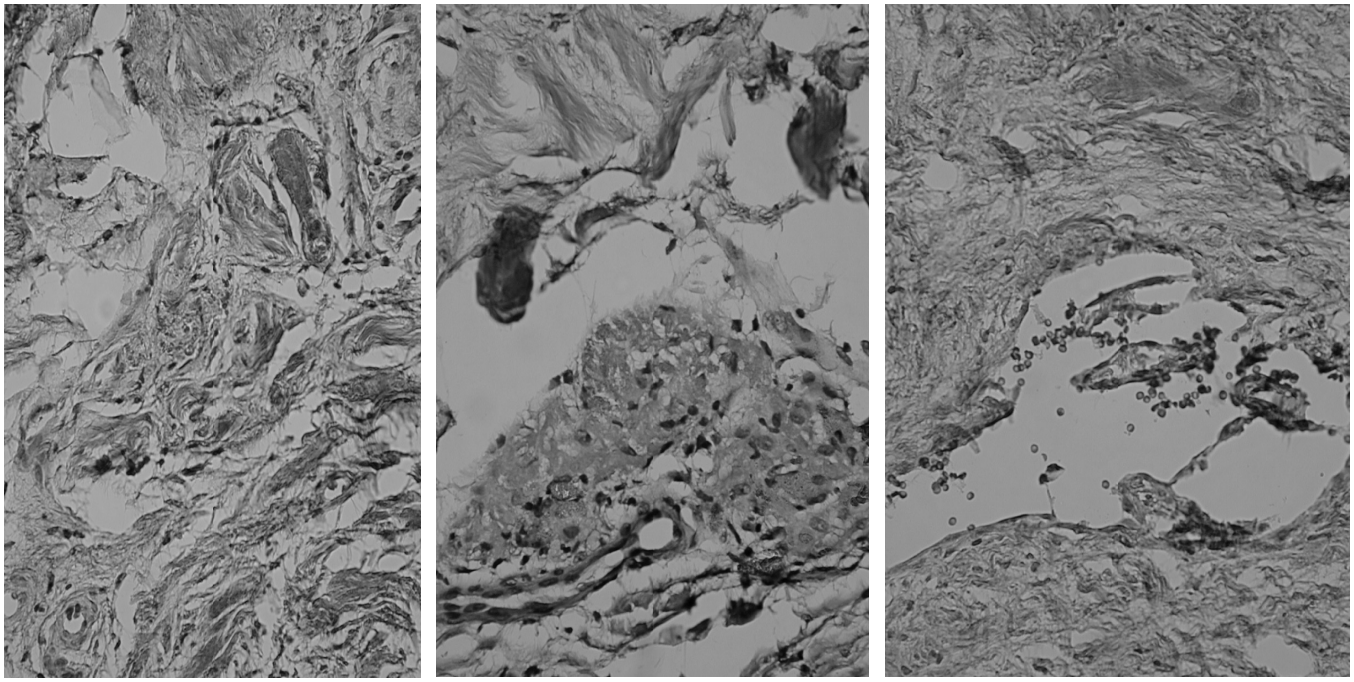

Fig. 5-6-7. Skin biopsy of molluscoid pseudotumours (daughter, 25 years old) revealing proportional increase in elastic fibers consistent with EDS.

Discussions:

Diagnosis of EDS in this family is based upon clinical findings, upon the family history, skin biopsy of molluscoid pseudotumours and other paraclinic investigations (MRI).

This three patients do not fit neatly into one of the specific types of EDS, a diagnosis is often delayed or overlooked. Specific diagnostic tests are available for some types of EDS in which there is a known biochemical defect, like in this case, but we don't have the possibility to test this. In the same time, the skin biopsy helps us to study the chemical makeup of the connective tissue. The biopsy involves removing a small piece of skin, under local anesthesia. To diagnose EDS it is necessary to have a good team of medical geneticists, pediatricians, rheumatologists, pathologists, cardiologists and dermatologists.

Since EDS is a genetic disorder it cannot be prevented. However, some of the complications of the disorder can be avoided to a certain degree. Prior to having children, individuals with EDS should consult their physicians and a genetic counselor to investigate the risks to themselves and to their potential children.

Clinic and genetic heterogeneity of the disease is very evident in this family, the three family members presenting clinical symptoms and comorbidities which made difficult the attempt to integrate them in a certain EDS type; these three cases presented a various clinical expression and severity. Another particularity is also represented by the presence and high frequency of associated spontaneous bone fractures. Molecular investigations could probably explain the mechanism which associates Osteogenesis Imperfecta signs to EDS symptomps, but we couldn't perform these investigations for the time (9).

References:

1. Autio, P.; Turpeinen, M.; Risteli, J., Kallioinen, M.; Kiistala, U.; Oikarinen, A., Ehlers-Danlos type IV: non-invasive techniques as diagnostic support. *Brit. J. Derm.* 137: 653-655, 1997.
2. Barabas, A. P., Ehlers-Danlos syndrome type IV. (Letter) *New Eng. J. Med.* 343: 366, 2000.
3. Byers, Peter H. "Disorders of Collagen Biosynthesis and Structure." In *The Metabolic and Molecular Bases of Inherited Disease.* Vol. 3. 7th ed., edited by Charles R. Scriver, et al. New York: McGraw-Hill, Inc., 1995.
4. Beighton, P., et al. "Ehlers-Danlos Syndrome: Revised Nosology, Villefranche, 1997." *American Journal of Medical Genetics* In press.
5. Germain, D. P.; Herrera-Guzman, Y. : Vascular Ehlers-Danlos syndrome. *Ann. Genet.* 47: 1-9, 2004.
6. Gilchrist, D., Schwarze, U., Shields, K.; MacLaren, L.; Bridge, P. J.; Byers, P. H., Large kindred with Ehlers-Danlos syndrome type IV due

to a point mutation (G571S) in the COL3A1 gene of type III procollagen: low risk of pregnancy complications and unexpected longevity in some affected relatives. *Am. J. Med. Genet.* 82: 305-311, 1999.
7. Pope, M. F., and Burrows, N. P., Ehlers-Danlos Syndrome has Varied Molecular Mechanisms, *Journal of Medical Genetics.* 34 (1997): 400
8. Kroes, H. Y.; Pals, G.; van Essen, A. J.: Ehlers-Danlos syndrome type IV: unusual congenital anomalies in a mother and son with a COL3A1 mutation and a normal collagen III protein profile. *Clin. Genet.* 63: 224-227, 2003.
9. Schwarze, U.; Schievink, W. I.; Petty, E.; Jaff, M. R.; Babovic-Vuksanovic, D.; Cherry, K. J.; Pepin, M.; Byers, P. H., Haploinsufficiency for one COL3A1 allele of type III procollagen results in a phenotype similar to the vascular form of Ehlers-Danlos syndrome, Ehlers-Danlos syndrome type IV. *Am. J. Hum. Genet.* 69: 989-1001, 2001.

Correspondence to:
Puiu Maria,
Martir O Munteanu Street, No. 9,
Timisoara 300360,
Romania
Phone: +4-0256-226824,
E-mail: maria_puiu@umft.ro