

Ehlers-Danlos syndrome

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In 2001, Schalkwijk *et al.* described, in eight patients from five families, a new autosomal recessive type of Ehlers-Danlos syndrome (EDS), caused by mutations in the *tenascin-X (TNXB)* gene and leading to a total deficiency of tenascin-X.¹ Since then no other patients with tenascin-X deficiency have been published; apparently it is a rare type of EDS. This new type of EDS can be differentiated from the classic type, which it resembles most, by its mode of inheritance (autosomal recessive *vs* autosomal dominant) and the absence of abnormal scarring, which is one of the key features in the classic type of EDS.

Remarkably, this new type is associated with congenital adrenal hyperplasia when it is due to a deletion encompassing the *CYP21* gene.^{1,2}

EDS consists of a group of inherited connective tissue disorders, mainly characterised by generalised joint hypermobility (= Beighton hypermobility score of 5 or more), skin hyperextensibility (measured at the volar side of the

underarm and/or at the flexed elbow), easy bruising and skin fragility (ranging from easy tearing after minor trauma to thin, broad scars and soft and velvety skin). It exhibits an enormous clinical and genetic heterogeneity. The monography by Beighton was the first comprehensive study of the syndrome and is still worth reading.³ In the latest classification six types are recognised (see *table 1*).⁴ EDS is not rare with an estimated prevalence of 1/5000. More than 90% of patients have either the classic or the hypermobility type.⁵

The classic type of EDS is characterised by all the main EDS features, namely hyperextensibility of the skin, broad and thin scarring ('cigarette-paper' scars), generalised joint hypermobility and easy bruising. Aortic dilatation and dissection is a rare complication of this EDS type. Well-known complications are recurrent (sub)luxations with chronic joint pain and early osteoarthritis, hiatus hernia, anal

Table 1
Villefranche classification of Ehlers-Danlos syndrome

| NEW NAME | OLD NAME | INHERITANCE | MUTATED GENES |
|----------------------|---|-------------|---------------------------------|
| Classic type | Gravis = type I Mitis = type II | AD | <i>COL5A1, COL5A2</i> |
| Hypermobility type | Hypermobile = type III | AD | <i>Unknown; ?TNXB?</i> |
| Vascular type | Arterial-ecchymotic = type IV | AD | <i>COL3A1</i> |
| Kyphoscoliosis type | Ocular-scoliotic = type VI | AR | <i>Lysyl-hydroxylase</i> |
| Arthrochalasia type | Arthrochalasia multiplex congenita = type VIIA and type VIIB | AD | <i>COL1A1, COL1A2</i> |
| Dermatosparaxis type | Dermatosparaxis = type VIIC | AR | <i>Procollagen, N-peptidase</i> |

AD = autosomal dominant, AR = autosomal recessive.

prolapse, cervix uteri insufficiency with premature labour as a result and cicatricial hernia. There is a large interfamilial and intrafamilial clinical variability. The male-to-female ratio is almost equal to one. In about 50% of cases a mutation can be detected in cultured fibroblasts in the *COL5A1* or *COL5A2* genes.

The hypermobility type of EDS has generalised joint hypermobility and mildly hyperextensible and/or soft and velvety skin as its main features. The main problem is the joint hypermobility with its sequelae, recurrent (sub)luxations of mainly shoulder, patella and jaw, chronic joint pain which can be severe and invalidating, and early arthrosis. Complications related to internal organs are extremely rare. It should be distinguished from the benign joint hypermobility syndrome (BJHS), which lacks the skin symptoms of EDS. However, there is much debate whether BJHS and the hypermobility type of EDS are not one and the same disorder.⁶ Personally, I adhere to the strict definition of BJHS, namely generalised joint hypermobility with Beighton scores >5, joint pain during a longer period in several joints and absence of skin features. Recently, Zweers *et al.* reported their tenascin-X findings in two groups of patients.⁷ First, the haploinsufficient family members (n=20, mainly siblings, children, parents) of their patients with absent tenascin-X due to homozygous or compound heterozygous *TNXB* mutations: in this group, nine out of 14 women – and none of the six males – showed generalised joint hypermobility and four of these nine women also had a velvety skin. The second group consisted of 80 hypermobility type EDS patients, diagnosed by a medical specialist and recruited through the Dutch EDS patient organisation. In six (7.5%; all females) of these, tenascin-X haploinsufficiency was detected. Four of these six patients were examined: two had Beighton scores <5 and no abnormal skin, while of the two with Beighton scores >5, one had normal skin. What does this tell us? Firstly, that probably quite a few of the 80 hypermobility-type EDS patients do not have the hypermobility type of EDS nor the strictly defined BJHS, secondly, that a better controlled study is needed to clarify the role of tenascin-X in hypermobility disorders, and thirdly that most likely skin extensibility and joint mobility is the end result of the involvement of many genes and exogeneous factors ('multifactorial'). This is illustrated in among other ways by the fact that haploinsufficiency for tenascin-X does exist without phenotype, for a presumed autosomal dominant disorder far too many patients are sporadic (= not familial) and almost all patients with the hypermobility type of EDS and BJHS are female.

The vascular type of EDS is more rare than the two previous ones but it is the most serious and life-threatening of all. Thin skin due to lack of subcutaneous fat with prominent venous pattern and a peculiar face and easy bruising are

hallmarks as well the easy rupturing of internal organs as the large arteries, large intestines and uterus. Pregnant women with the vascular type of EDS are at an increased risk for severe complications. It is caused by mutations in *COL3A1* gene (cultured fibroblasts), which are detectable in nearly all patients.

The other three types are even rarer and will not be discussed in detail. Apart from these six EDS types and the new tenascin-X deficient type, there are more poorly defined EDS types and single family 'types'.⁴ From clinical practice it is known that not every patient with an EDS phenotype can be classified in one of the well-defined types.

EDS is diagnosed and classified on the basis of history, family history and physical examination with laboratory confirmation when possible and indicated, at the protein level (tenascin-X in serum, collagen 1, 3 and 5 in fibroblasts) and/or at the molecular level (see text and *table 1*).

Interestingly, some often heard complaints are not readily found in textbooks on EDS: easy fatigue is one of these as is the ineffectiveness of local anaesthesia; the former is particularly clinically important and often distressing. Single reports on EDS patients with various clotting abnormalities (for example von Willebrand disease, factor IX deficiency, factor XIII deficiency, platelet release defect, fibronectin deficiency) have been published, but the cause of the easy bruising is much more likely to be due to vessel wall fragility than to a coagulation defect.⁵

Management of EDS is largely supportive (e.g. physiotherapy, ergotherapy, rehabilitation) and preventive (e.g. surgical precautions, avoiding certain professions and sports, avoiding overweight); it is rarely surgical (e.g. arthrodesis). Genetic counselling is part of the management. Differential diagnosis of EDS includes other connective tissue disorders such as Marfan's syndrome, cutis laxa and osteogenesis imperfecta, but also a host of other diagnoses depending on the presenting complaint/symptom. Since it is also of great importance for the internist to recognise EDS in order to start timely management and to avoid unnecessary investigations, it is therefore wise of the editors of the Netherlands Journal of Medicine to publish the paper by Peeters *et al.*,⁸ not so much to draw attention to this rare type of EDS, but more to EDS in general.

NOTE

There is an active Dutch patient organisation (Vereniging van Ehlers-Danlos patienten, www.ehlers-danlos.nl). In the Netherlands, the molecular and protein diagnostics of EDS (for types see *table 1*) are performed at the VU University Medical Center, Department of Clinical and Human Genetics, Laboratory for DNA and Protein Diagnostics, Amsterdam, head Dr G.Pals.

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