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How to Diagnose Clinically with Certainty the Ehlers-Danlos Disease

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Abstract

Ehlers-Danlos is a hereditary disease of the connective tissues responsible for numerous clinical manifestations due to their fragility and dysproprioception, the origin of which is the distortion of the signals that these tissues send to a nervous system that is spared by the pathological process. The frequency of this disease, which is transmitted to all the children of an affected person, is very underestimated and could concern 2% of the population worldwide.

We were able to identify 79 signs in total. We chose 9 signs among the 20 most frequent signs for their representativeness of tissue fragility or dysproprioception, namely joint pain, fatigue, clumsiness, joint instability, changes in the structure of the skin (thin, stretchable or fragile), joint hyperlaxity, gastroesophageal reflux disease, frequent bruising, hyperacusis. The presence of these 9 signs was sought in two control groups, a first one of 826 "normal" subjects assessed during a systematic occupational medicine consultation and a second one of 206 patients consulting a general practitioner or a specialist without preliminary diagnosis. It is observed that 98% of the 853 patients affected by the disease have at least 5 of these 9 signs but that 99.6% of the 826 normal subjects and 98.1% of the 206 consultant patients do not have them. Diagnosing Ehlers-Danlos disease is therefore possible with certainty by a clinical examination that highlights at least 5 of the 9 signs that we have described in this work.

Keywords: *Ehlers-Danlos; Hereditary Disease; Hyperlaxity; Multiple Pain; Proprioception; Dystonia; Mental Hyperactivity; Working Memory; Parental Violence; Arterial Aneurysm; Spontaneous Fractures; Diabetes Insipidus*

Identification of the main signs of the Ehlers-Danlos disease

This diffuse connective tissue disorder is largely poly symptomatic, confusing physicians and complicating diagnosis. They have great difficulty accepting that such different symptoms and signs can have a single cause and be diverse expressions of the same disease.

The development of a medicine which tends to identify diseases by groups of organs with biological criteria and medical imaging for each one further accentuates this tendency and very often leads to diagnostic errors. The situation is made even more complex by the symptomatic variations, such as age of onset and severity, which are expressed differently within the same family, even in homozygous twins, as we have observed in several times.

The discovery of other unexpected clinical manifestations in a patient presenting the two "historical" signs of Ehlers-Danlos disease (joint hyperlaxity and excessive skin stretch), led us to systematically look for them in other hyperlaxed patients.

We were able to identify 79 signs in total. We chose 9 signs among the 20 most frequent signs for their representativeness of tissue fragility or dysproprioception, namely joint pain, fatigue, clumsiness, joint instability, changes in the structure of the skin (thin, stretchable or fragile), joint hyperlaxity, gastroesophageal reflux disease, frequent bruising, hyperacusis.

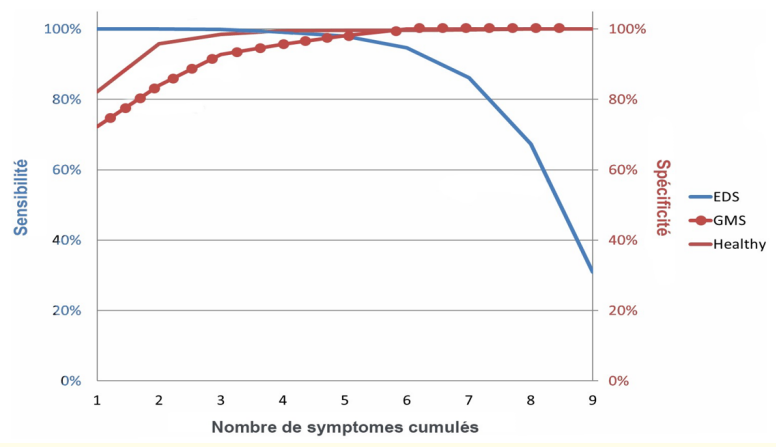
The presence of these 9 signs was sought in two control groups, a first one of 826 "normal" subjects assessed during a systematic occupational medicine consultation (group "Healthy") and a second one of 206 patients consulting a general practitioner or a specialist without preliminary diagnosis (group "GMS"). The results of this research of these 9 signs are shown below in the form of a table. The results, compared with a group of 853 Ehlers-Danlos patients (group EDS), are shown in the table below.

	Healthy	GMS	EDS
Total number of patients for each group	826	206	853
Total number of patients presenting 5 signs out of the 9 signs	3	4	836

It is observed that 98% of the 853 patients affected by the disease have at least 5 of these 9 signs but that 99.6% of the 826 normal subjects and 98.1% of the 206 consultant patients do not have them.

This means that the search for 5 signs out of the 9 makes it possible to detect the vast majority of EDS patients (we speak of sensitivity) but only produces very few false positives in control patients (we speak of specificity).

The result are also visible in the following graph.



Graph

This graph explains why 5 signs out of the 9 are enough to identify the disease. This is the optimal number to achieve both a good sensitivity and a good specificity. Choosing a higher threshold would have resulted in excellent specificity, i.e. no false positives, but poor sensitivity, i.e. many false negatives. Conversely, choosing a threshold that is too low results in excellent sensitivity, i.e. no false negatives, but poor specificity, i.e. many false positives.

All of this clearly shows that it is possible to make the diagnosis of Ehlers-Danlos disease with certainty by showing 5 clinical signs out of a small number of 9 characteristic signs.

Nine clinical signs to diagnose the Ehlers-Danlos disease

The nine signs taken into consideration in the study mentioned in the previous paragraph are discussed below.

The pains

Pains are diffuse (joints, skin, thorax, abdomen, uterus, migraines, tinnitus, dazzling), they are permanent with painful attacks sometimes localized (feeling of "being stabbed", feeling of being burned by a red hot iron, feeling suddenly teared or crushed, feeling hit by electric shocks, feeling like something is bursting…). They vary from day to day and from time to time throughout the day.

Fatigue

It is considered by many patients to be the most disabling symptom. It is not related to lack of sleep and appears more as the proprioceptive "feeling" of fatigue or exhaustion, rather than that of bodily fatigue.

Bleeding

Bleeding is linked to the fragility of the capillaries and probably to that of the platelets and not to a coagulation disorder. These manifest through bruises, gingivorrhagia, epistaxis (especially in children), menorrhagia, metrorrhagia, intestinal bleeding, urinary tract bleeding.

Changes to the skin and its fragility

An excessive stretching of the neck or of the arm is an historical and well-known sign of the disease. Other manifestations must be added to this category: softness of the skin on contact, transparency objectifying the venous networks, abrasions, difficulties of healing with unsightly scars, importance of stretch marks, absence of wrinkles, smooth appearance of the face giving a young appearance. The feeling of an electric shock when touching a door, a shopping cart or the skin of another person is also a common sign of thinness of the skin.

Joint hyperlaxity

It affects all the joints and particularly the shoulders, as shown by the Cypel test (obtaining a passive abduction of 120 degrees by blocking the scapula).

Dislocations and sprains

They mainly concern the shoulders, knees, ankles, fingers, it can be simple joint crunches without gravity for joint wear which are the result of a subluxation.

"Clumsiness"/motor disorders (dysproprioception/dystonia)

Unintentionally hitting against a door or a piece of furniture when walking, involuntarily dropping objects, falling.

Hyperacusis

Hyperacusis is responsible for hearing discomfort but also often for exceptional hearing acuity, often with a "perfect pitch" and a gift for music.

Gastroesophageal reflux

The observation of these signs in the family (ascendants, collaterals and descendants) constitutes proof of their hereditary nature and contributes to the diagnosis [1-6].

Conclusion

Knowledge and identification of this disease, with its multiple and disabling clinical expressions, is too often limited to the sole search for the presence of hyperlaxity. This restricted vision leads to a very large number of errors due to the ignorance of other signs (hematological, digestive, urinary vascular, cognitive, etc.) with sometimes catastrophic medical and social consequences. Among the most serious of them we find the false accusation of parental violence causing the removal of a child affected by EDS from his family or a diagnosis of Münchausen's disease when diagnostic procedures are rendered endless and unsuccessful because of the ignorance of the disease by the medical professionals.

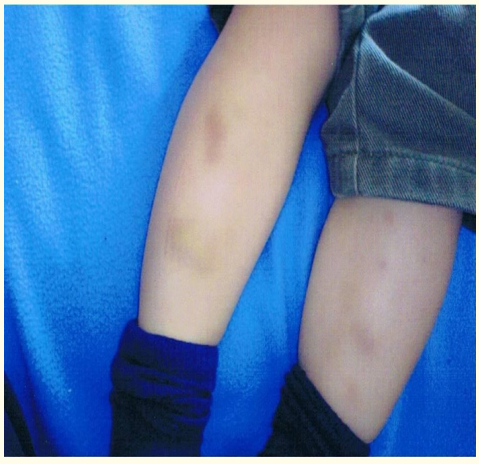


Figure: *Spontaneous Ecchymosis in a child affected by EDS.*

Several causes contribute to medical wanderings:

- The symptoms presented are those that the doctors "don't like": fatigue, diffuse pain, nausea, constipation, sprains, back pain, urinary or fecal incontinence, hemorrhoids, allergic symptoms, etc.
- The false reputation of being a rare disease (leading to a rare evocation of its diagnosis) while it is a very common disease. This false reputation for rarity is commonly associated with the prejudice that its diagnosis is necessarily made on a genetic or biological test.
- The lack of contribution of imaging and biology to the diagnosis. A special mention should be made for skin biopsy with ultrastructural analysis by electron microscopy which, curiously, is very little used outside of Belgium.

Diagnosing Ehlers-Danlos disease is therefore possible with certainty by a clinical examination that highlights at least 5 of the 9 signs that we have described in this work. This approach facilitates its screening in all countries, even the poorest in medico-technical means.

Conflict of Interest

Authors declare no conflict of interest.

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