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CLINICAL DIAGNOSIS OF EHLERS-DANLOS SYNDROME. NEW FUNDAMENTAL INSIGHTS INTO THE CLINICAL SETTING.

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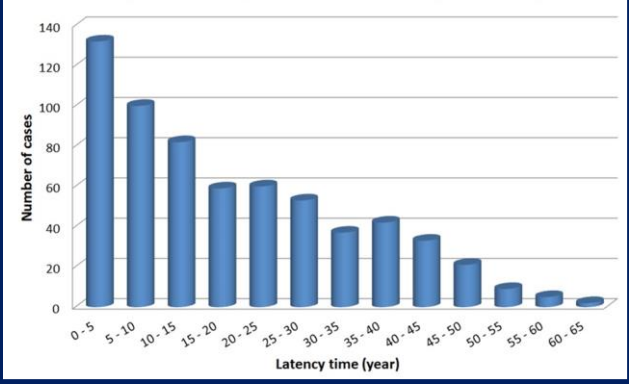
Introduction

If we trace this disease's description history through the successive interests of dermatologists (*cutis laxa*), rheumatologists (joints hypermobility), geneticists (research of collagens mutations and genetic classification), we better understand why such a **frequent pathology** is **never diagnosed** or with an average **delay of more than 20 years** after the onset of the first signs.

Histogram of the latency time between the first symptoms of the EDS and its diagnosis (636 evaluations).



During the last decades, studies of the Ehlers-Danlos syndrome have added many signs/symptoms to the stretchy skin and generalized joints hypermobility making EDS a multifaceted systemic disease (Grahame 1960). This controlled study aimed to identify the smallest number of additional clinical signs enabling EDS diagnosis with certainty.

Patients and methods.

We prospectively assessed **853 EDS patients** attending our outpatient ward between June 2014 and June 2017. They all met the 1997 **Villefranche criteria**. These

patients had **62 clinical signs/symptoms**. The most frequent are: Fatigue 97%, Hypermobility 95%, Arthralgia 95%, Finesse and skin transparency 94%, motor dysproprioception 89%,Meno/metrorhaggia 87%, Bruisings 86% , Migraines 83%, Visual fatigue 83%, Plantar Contractions 82%, Dyspnea 82% Temperature dysregulation 80%, Hyperacousia 79%, Increased skin stretching 79%, Sprains or pseudo-sprains 78%, Attention deficit 77%, Pseudo-Raynaud phenomenon 77%, Difficulty scarring 76%, Cutaneous hyperesthesia 76%, Genital pains 74%, Abdominal pains 74%, Gastroesophageal reflux 74%, Meteorism 74%, Hyperhidrosis 73%, Decreased working memory capacity 73%; Hyperosmia 72%, Vertigo 71%...

Each clinical problem was **quantified** by a **0-4 Likert scale** before to be classified into one of the following sections:

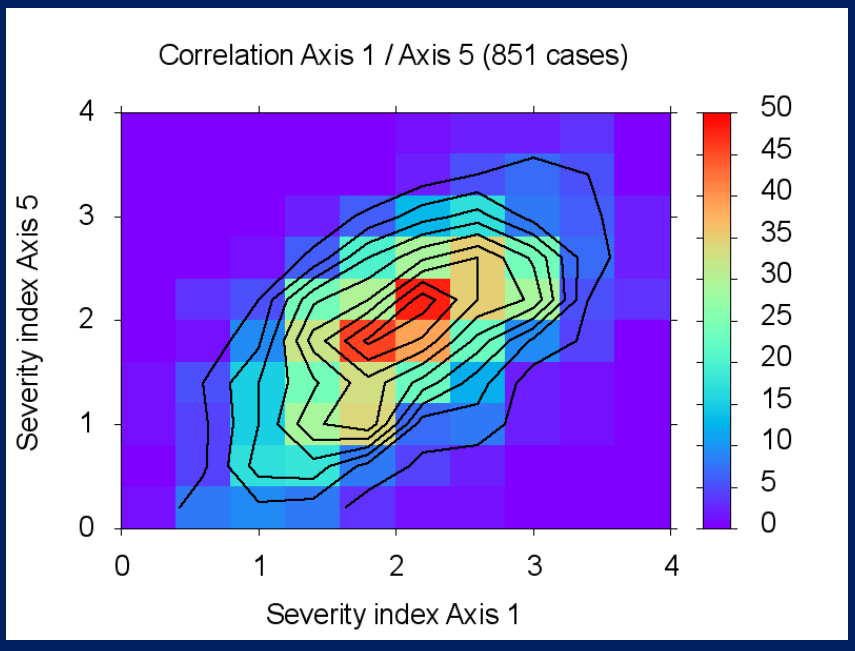
- **Axis 1** : *Fragility of connective tissue - Skin, mucous membranes & teeth*
- Axis 2 : *Fragility of Connective Tissue - Hemorrhagic Syndrome*
- **Axis 3** : *Proprioceptive disorders - Joints & motor skills*
- **Axis 4** : *Proprioceptive disorders - Dysautonomia*
- **Axis 5** : *Proprioceptive Disorders - Perception Disorders*
- Axis 6 : Alterations of cognitive functions

The 62 items were also evaluated in the **control groups** included **826 healthy subjects** and **206 patients with rheumatic conditions unrelated to EDS**

Results

1-Comparison between the different axis.

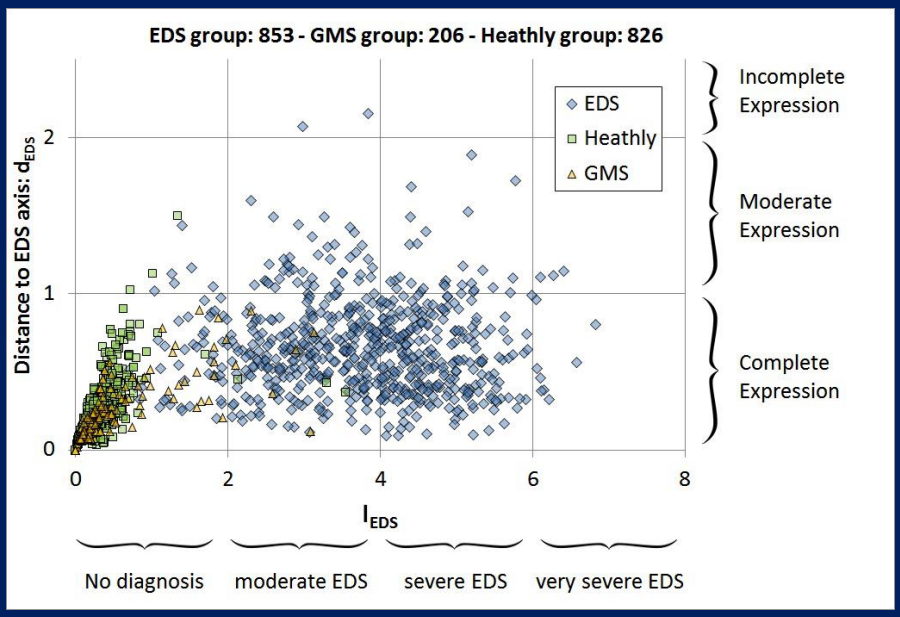
Statistical analysis showed that distributions of severity indices on **1, 3, 4 and 5** are similar and correlated two by two.



The comparison between these groups disclosed a very significant dissociation with the two other groups. Further, the **1, 3, 4 and 5 groups were very homogeneous**.

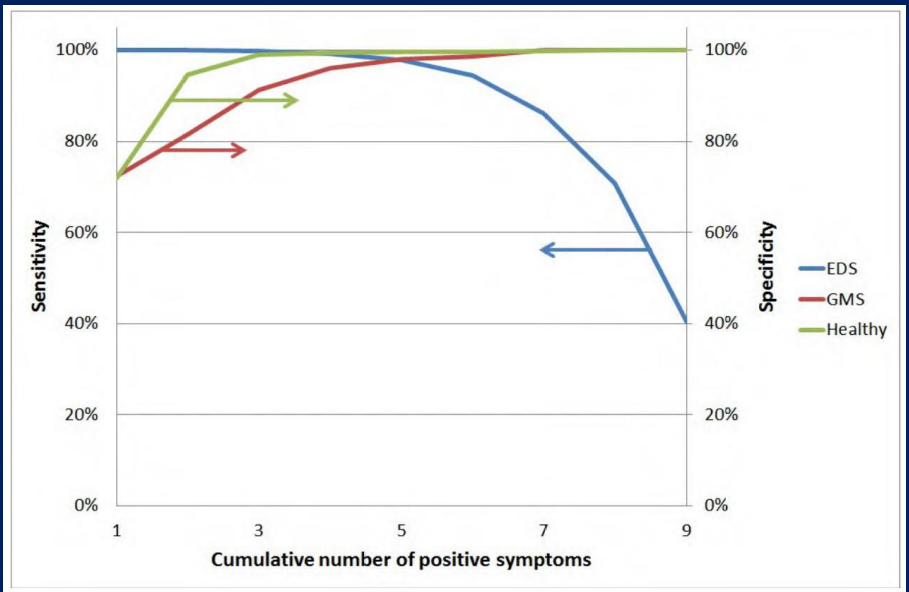
This homogeneity is a strong argument in favor of the **uniqueness of Ehlers-Danlos disease** and goes against its fragmentation into different types as suggested.

2-Comparison between EDS patients and control groups (Heathly and GMS/General Medicine & Specialities)



There is a very significant dissociation between the positioning of healthy controls and MGS groups, on the one hand, and the SED patient group, on the other hand. We also note the very strong homogeneity of the EDS group. Indeed, by gathering the data in three categories, according to their severity (IEDS) of 0 to 8, one observes the following distribution (in percentage for each group): **IEDS <2**: 7.3% of the EDS group, **97.1%** of the MGS group and **99.6%** of the control group, **IEDS> 2**: 92.7% of the EDS group, 2.9% of the MGS group and 0.4% of the control group.

The data allowed the design of a **mathematical model** that gives the EDS diagnosis with a **sensitivity of 99.6%** and a **specificity of 97,1%** when the patient exhibits **five** out the following **nine** items: **diffuse pains**, **fatigue**, **thin skin**, **proprioceptive motor disorder, joint instability**, **hypermobility**, **gastroesophageal reflux**, **easy bruising**, and **hyperacusis**.

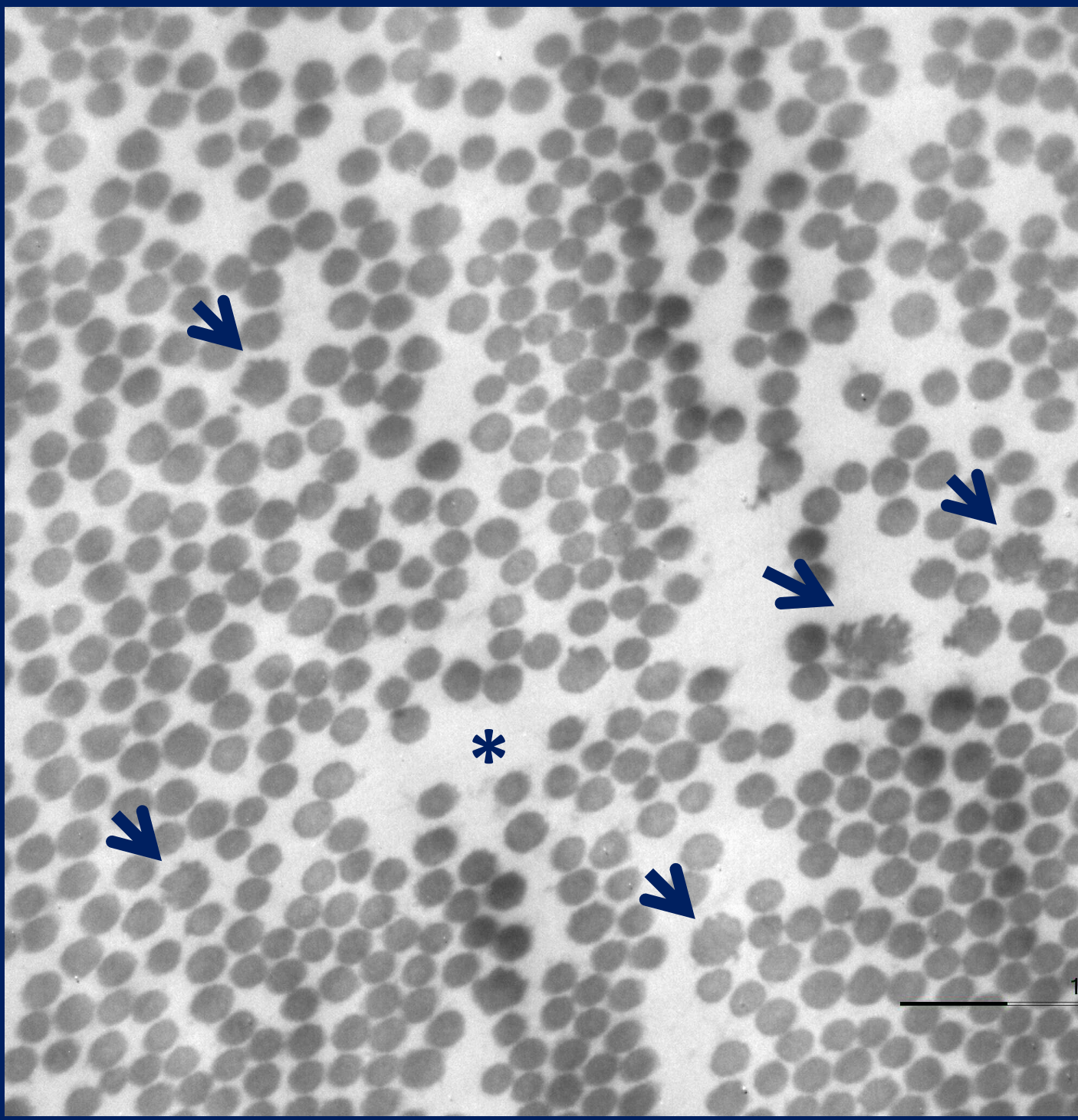


Specificity and sensitivity of the EDS quick diagnostic tool.

Contribution of histology (electronic microscopy).

Pr**. Hermanns-Lê Trinh**

Two hundred subjects with at least five out of the nine signs all had common abnormalities of their dermal collagen network including variability in the diameter of collagen fibrils, flower-like collagen fibrils, and dense interstitial granulofilamentous deposits.



Hereditary transmission of EDS

If a father or a mother suffering from EDS, all children were also suffering from EDS. Recently, we verify that with 45 families examined in ELLAsanté Center in Paris.

Conclusions

Our clinical algorithm enables **EDS diagnosis** early and **with certainty**. It has several potential advantages. For instance, it might help confirm the hereditary character of EDS, it might too obtain **specific treatments** and social supports, and deny **false accusations of parental abuse** (in forensic medicine).

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