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Research Article

Ehlers-Danlos Syndrome (EDS) - Contribution to Clinical Diagnosis - A Prospective Study of 853 Patients

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Abstract

Background and Objective: Ehlers-Danlos syndrome (EDS) is a connective tissue disease which is diagnosed very late or never due to insufficient description. The goal of this work is to offer a new description with reliable clinical diagnostic criteria.

Methods: 853 consecutive EDS patients, examined prospectively between September 01, 2009 and September 2017, in an EDS dedicated consultation, are presented. Severity of symptoms and signs are quantified according to a Likert scale from 0 to 4. They were grouped into six axes considering two pathophysiological mechanisms: tissues fragility and proprioceptive disorders. The 853 EDS patients were compared to two control groups, one of healthy subjects, the other of patients coming to see a doctor for a pathology other than Ehlers-Danlos syndrome.

Results: Comparative statistical analysis of the axes establishes a formal correlation between four of them (fragility of skin, mucous membranes and teeth, dysautonomia, joints and motor skills, perceptions disorders), proof that their clinical manifestations belong to the same disease with different expressions. The clinical data comparison of the 853 EDS cases to those of a normal population of 814 people and a population of 206 people consulting for a disease other than EDS demonstrates that the symptoms sustained for the identification of the Ehlers-Danlos syndrome are specific. This allowed the construction of a mathematical model with which it is possible to establish meaningful lists of signs allowing a diagnosis of certainty. We have compiled a list of 9 signs (joints pains, fatigue, motor dysproprioception, joint instability, skin fragility, hypermobility, gastro-esophageal reflux, ecchymosis, hyperacusis) which lead to the diagnosis if 5 of them are present with a sensitivity of 99.6% and a specificity of 98%. The presence in the family of similar cases shows the hereditary nature of the disease.

Conclusion: Our group of patients is clinically homogeneous, which suggest the uniqueness of Ehlers-Danlos syndrome with a simplified clinical diagnosis.

Keywords: *Ehlers-Danlos Syndrome; Hereditary Disease; Clinical Diagnosis; Epidemiology; Mathematical Model; Chronic Pains; Fatigue; Dysautonomia; Dystonia; Hemorrhagic Tendency; Hypermobility*

Introduction

Initially described by dermatologists (Tchernogoubov, Moscow, 1891, Ehlers, Copenhagen, 1900) who emphasized cutaneous manifestations and joint hypermobility [1,2], Ehlers-Danlos syndrome (EDS) is usually diagnosed with a very big delay figure 1. Consequences are important for these patients with very fragile connective tissues who are exposed to severe complications, most often iatrogenic. Moreover, deprived of diagnosis, they ignore that they transmit the disease. There is widespread misunderstanding of clinical signs of a disease which is frequently underestimated. Our goal is to complete its description and offer clinical diagnosis of this hereditary disease for which molecular genetics cannot, today, provide an answer in most of cases. For this, we rely on the monitoring of 2,764 patients, examined between September 1, 2009 and September 1, 2017 as part of a dedicated consultation. This is a prospective study of 853 outpatients. Inclusion criteria were new patients diagnosed with EDS by a small team using the same questionnaire and Brighton test [3]. Statistical analysis compared to two control groups, one of healthy subjects, the other of outpatients coming to see a doctor for a pathology other than Ehlers-Danlos syndrome.

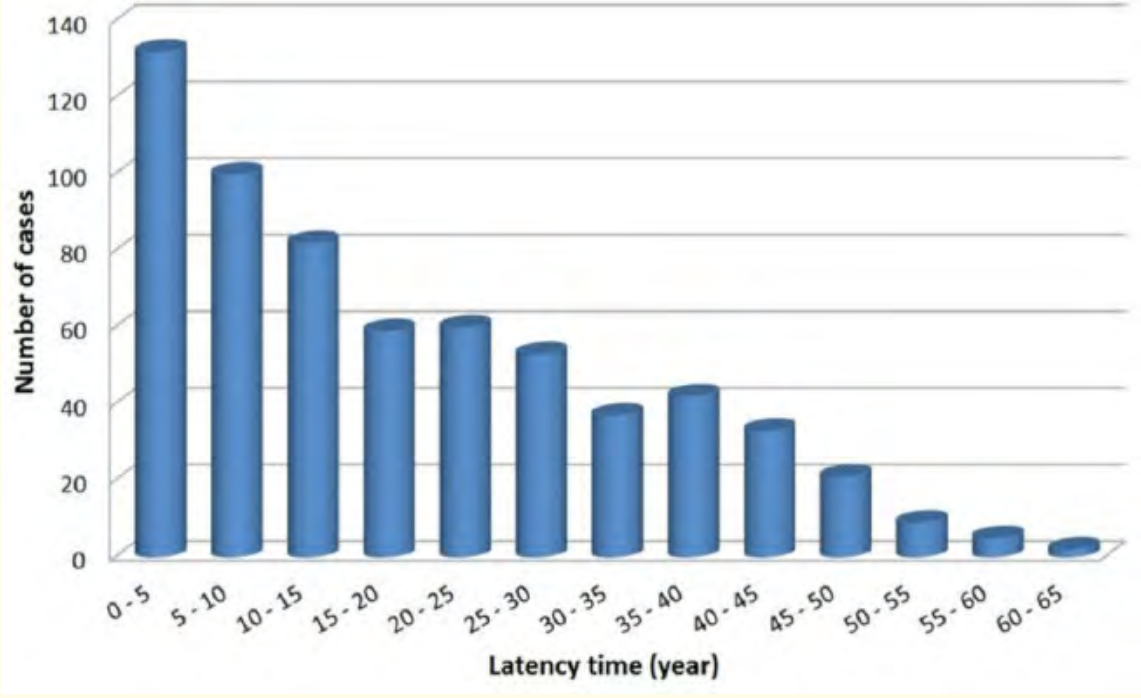

Figure 1: *Histogram of the latency time between the first symptoms of the EDS and its diagnosis (636 evaluations).*

Material and Methods

This prospective study is based on three groups of patients.

The first group (EDS group) is composed of 853 consecutive patients with Ehlers-Danlos syndrome, diagnosed by a small team using the Brighton test and examined between June 1, 2014 and June 1, 2017. They were diagnosed upon lifelong symptoms. The mean age is 32.0 years ± 16.5; it is composed of 165 men (M) and 688 women (W) (W/M ratio: 4.2). The extreme ages are 1 year and 71 years old. None of them were genetically tested.

The second group (GM group), examined by the same team, is composed of 206 patients consulting in general or specialty medicine, for a pathology other than Ehlers-Danlos syndrome. In this group, the mean age is 55.3 years ± 16, at; it includes 109 men and 97 women (W / M ratio: 0.9). The extreme ages are 5 years old and 92 years old.

The third group (control group) is composed of 826 last persons examined from a cohort of 3,528 tertiary sector employees, during a systematic occupational health consultation. In this group, the average age is 31.4 years ± 8.3. It comprises 408 men and 418 women (W/ M ratio: 1.0). The extreme ages are 20 and 62 years old. We identified three individuals with a significant EDS symptomatology in this group.

Sign	EDS	MGS	OM
Fatigue	97%	14%	7%
Hypermobility	95%	4%	7%
Arthralgia	95%	19%	3%
Finesse and skin transparency	94%	5%	2%
Sleeping problems	90%	13%	26%
Dys-proprioception	89%	1%	0%
Meno/metrorhaggia	87%	13%	11%
Myalgia / cramps	87%	11%	0%
Cutaneous Hemmoraghes	86%	4%	1%
Migraines or headaches	83%	5%	4%
Visual fatigue	83%	6%	3%
(Sub)-luxations	82%	1%	0%
Plantar Contractions	82%	3%	0%
Dyspnea	82%	11%	0%
Temperature dysregulation	80%	10%	2%
Hyperacousia	79%	2%	0%
Increased skin stretching	79%	1%	1%
Genital hemorrages	78%	7%	9%
Sprains or pseudo-sprains	78%	1%	2%
Attention deficit	77%	3%	1%
Pseudo-Raynaud phenomenon	77%	4%	1%
Difficulty scarring	76%	3%	0%
Cutaneous hyperesthesia	76%	4%	0%
Genitale pain	74%	4%	6%
Abdominal pain	74%	6%	3%
Gastroesophageal reflux	74%	9%	13%
Meteorism	74%	7%	19%
Hyperhidrosis	73%	6%	0%
Decreased working memory capacity	73%	5%	3%
Upper respiratory infections	72%	3%	23%
Hyperosmia	72%	4%	0%
Vertigo	71%	5%	4%

Table 1: *The most common signs in our EDS with 853 Patients having a frequency above 70% (34 out of 79 signs).*

Experience gained from consultations between 1998 and 2015 made it possible to construct an evaluation grid of 79 symptoms and clinical signs grouped into 16 families: pain, fatigue, sleep disorders, joint and motor disorders, cutaneous manifestations, autonomic dysfunction, cardiovascular alterations, hemorrhagic tendency, digestive and abdominal disorders, vesico-sphincter disorders, oral and dental changes, ENT manifestations, visual disturbances, respiratory manifestations, sexuality and procreation, and cognitive disorders. Each symptom or sign was quantified according to a Likert severity scale with 5 levels of severity: 0 (absent), 1 (discrete), 2 (moderate), 3 (important) to 4 (very important). This quantification takes into account clinical history of the patient. In this pathology, symptoms are changing as time goes by. We have selected as criteria for severity the highest severity observed, whatever the moment of observation. For example, a patient may have had a very significant joint hypermobility in his childhood and no longer have it at the time of the examination. The hypermobility of this patient will be rated 4 with the Likert scale while its current state would justify a rating of 0.

To be able to carry out a statistical study in patients with EDS, we have grouped the symptoms and signs of the syndrome on 6 axes by relying on the two notions of physiopathology at the origin of clinical manifestations: tissue fragility and dysproprioception.

- Axis 1: Fragility of connective tissue - Skin, mucous membranes and 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

A previous study (4) involving 626 patients made it possible to establish that only axes 1, 3, 4 and 5 were relevant for establishing an overall EDS severity scale (IEDS) and typicity (dEDS). Of the 79 symptoms initially proposed, only 62 were selected because of their severity (Likert severity scale: 2 or more) incidence. The data statistics from this first study are included in the 853 patients results of this study.

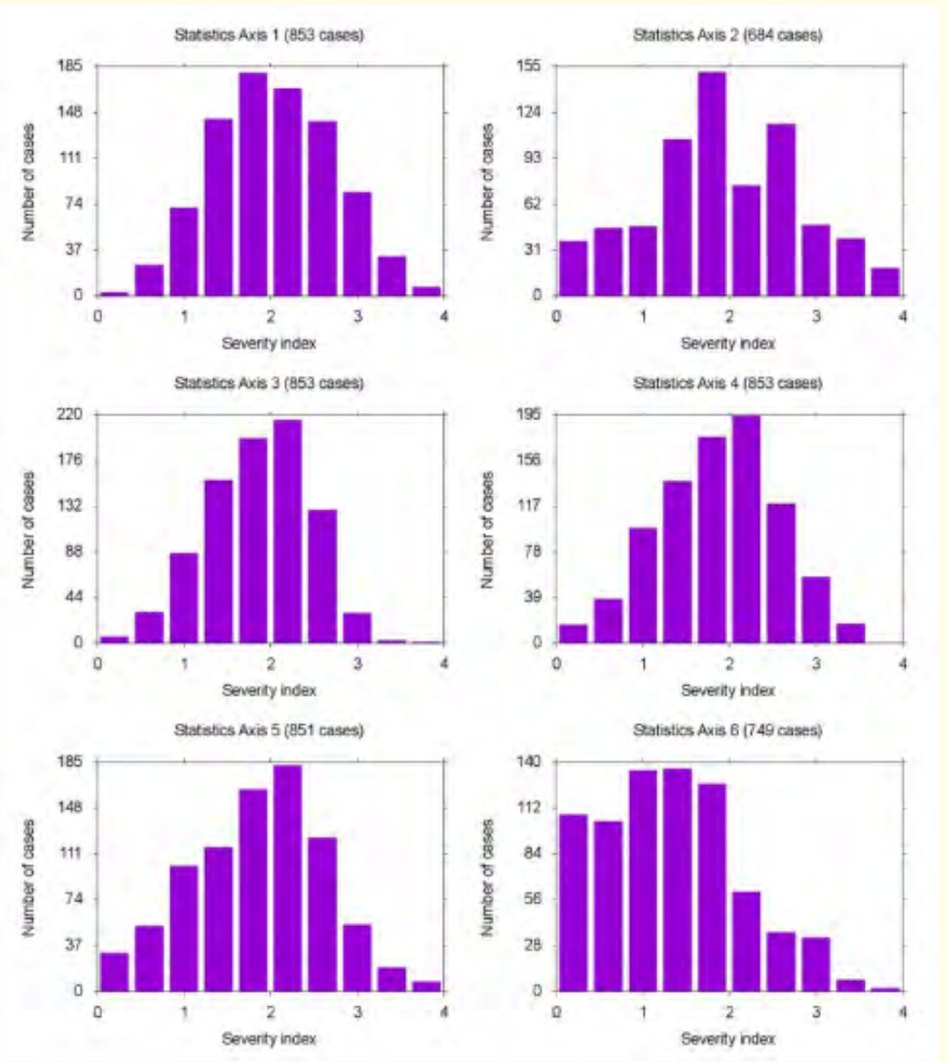

Figure 2: *This figure show clearly that the statistical distributions of axes 1, 3, 4 and 5 are similar. Axes 2 and 6 exhibit different distribution as explain in the present contribution and have been, for the present time, discarded for detailed statistical studies.*

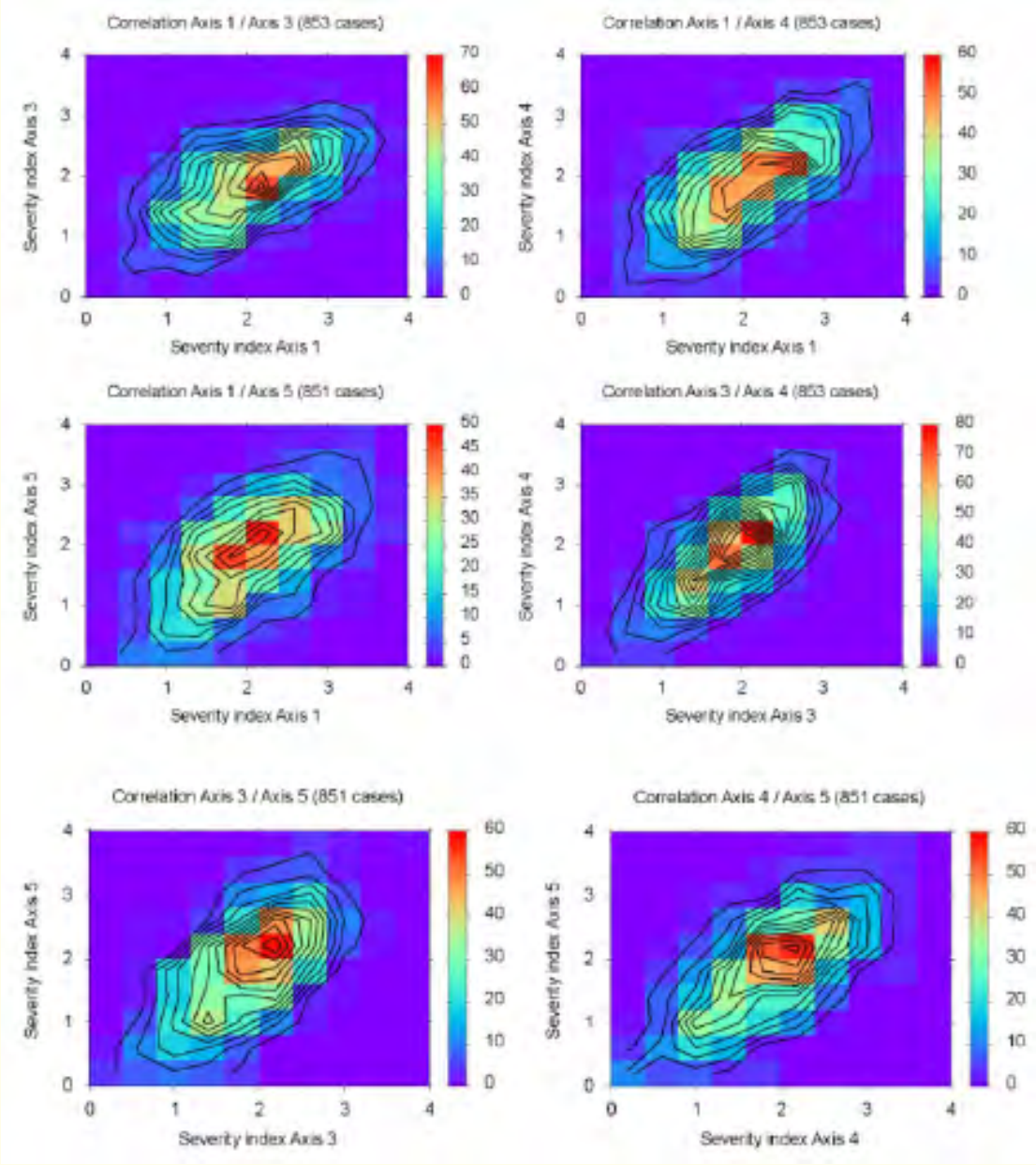

Figure 3: *The severity indexes of axes 1, 3, 4 and 5 are strongly correlated. Those 4 axes of diagnosis form a coherent whole. For an EDS patient, the severity index of axes 1, 3, 4 and 5 are strongly correlated.*

Results

Our mathematical modeling allows us to calculate each patient's index of severity. Statistical analysis shows that distributions of severity indices on axes 1, 3, 4 and 5 are similar and correlated two by two. Axes 2 and 6 are not correlated with the others. The lack of correlation is explained by the difficulty of clinically assessing the scores of hemorrhages and cognitive disorders with the Likert scale.

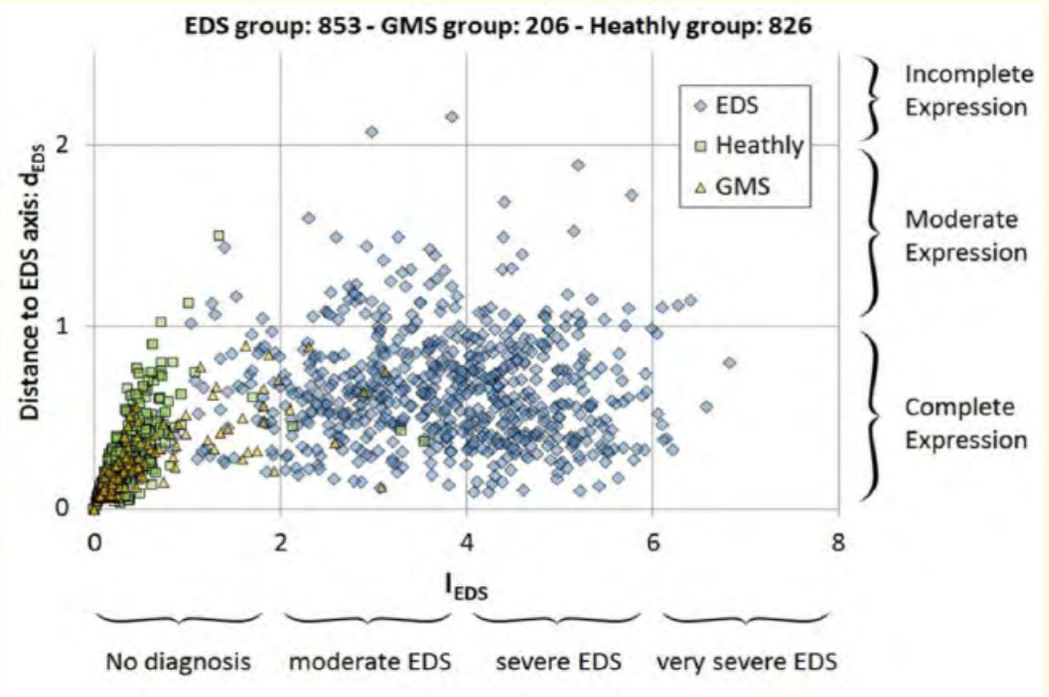

Figure 4: *EDS mapping the severity and symptomatic expression.*

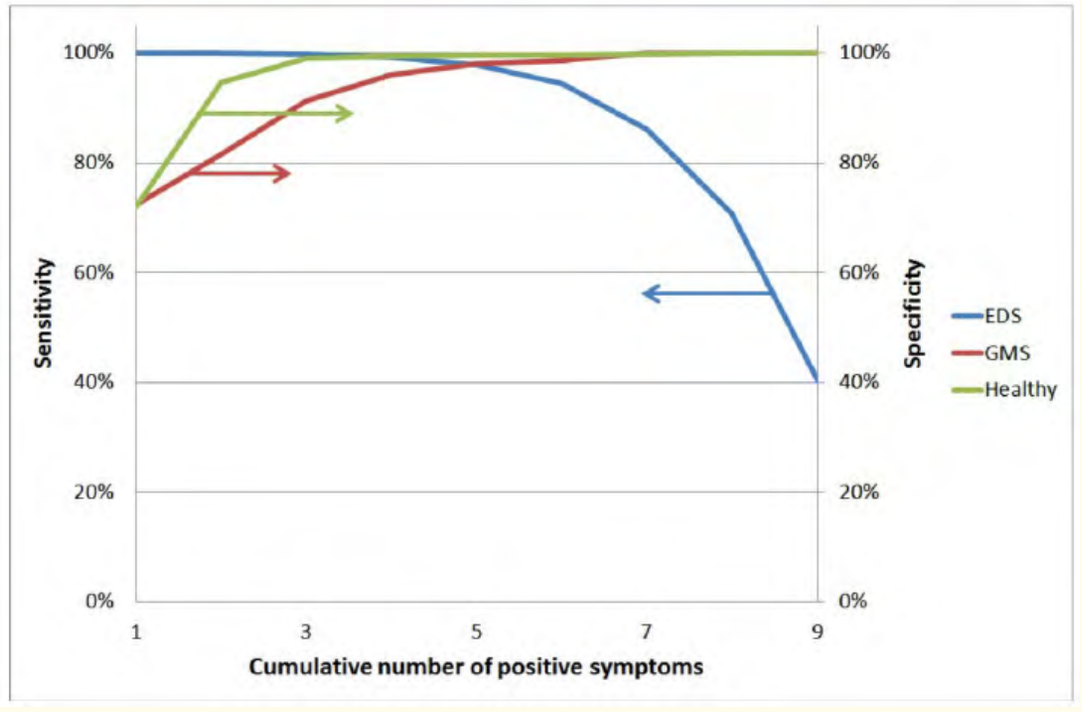

Figure 5: *Specificity and sensitivity of the EDS quick diagnostic tool. GMS (group of mpatient consulting a general practioner or a specialist.*

Figure 4 shows how the 853 cases of the study are positioned in the plan (IEDS, dEDS), the 826 healthy controls and the 206 patients consulting for another pathology. There is a very significant dissociation between the positioning of healthy controls and MGS groups, on the one hand, and the EDS patient group, on the other hand. We also note the very strong homogeneity of the EDS group. Indeed, by gathering the data of figure 2 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 GM group and 99.6% of the control group,
- IEDS > 2: 92.7% of the EDS group, 2.9% of the+ GM group and 0.4% of the control group.

There is a very high homogeneity of EDS patients who are very easily distinguished from the control group and the GM group in the plan (IEDS, dEDS). 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 [5].

Discussion

Our study is the first to clinically explore such a large group of patients with a diagnosis of Ehlers-Danlos syndrome. It shows a homogeneity of the grouping of very diverse clinical manifestations in their modality of expression. This is an original approach based on the clinic only with the assumption that patients who come to consult have a common pathogenetic base which originate from connective tissue abnormality.

We note (Figure 2) that 92.7% of patients in the EDS group are in the pathological area versus 0.4% of the control group and 2.9% of the GM group. Only 7.3% of EDS patients could be considered false positive (or subclinical). Of these 62 cases, 50 were received as part of a family consultation where other cases of Ehlers-Danlos were diagnosed. There remain 12 “false positives” (no family history and low severity index) or 1.4% of the cohort.

The clinical assessment scale is built on the assumption of a generalized somatosensory disorder. We note that our scale has characteristics like the Brighton criteria described by Grahame [3] which gives an important place to joint hypermobility. Our somatosensory approach allows a more global clinical method. In the control group, we observe that 4.1% (2.2% of men and 5.5% of women) of the population have a Beighton score greater than 4. On the other hand, according to clinical somatosensorial scale ECSS-62, we detect 0.4% of the general population with EDS hence a prevalence 10 times lower. This confirms better sensitivity of this approach. Our observations are consistent with bibliographic data highlighting a heterogeneous, multisystemic, digestive system [6,7], proprioception [8,9], neurovegetative system [10-12] disease and gynecological signs [13]. Our data confirm the polymorphic aspect of the symptomatology and highlight a correlation between the symptoms. This allows to conclude on homogeneity of our patient population. On the other hand, we have made an important place for cognitive disorders, which have not been sufficiently described so far.

We were able to demonstrate, using our mathematical modeling of the symptoms, and signs that the detection of 5 symptoms on the 9 selected makes possible to establish the diagnosis with a sensitivity of 98.0% and a specificity 98.1% versus the group of patients consulting in general or specialty medicine, for a pathology other than Ehlers-Danlos syndrome and 99.6% versus the control group of healthy people. The selected signs are: joint pain, fatigue, proprioceptive motor control disorders, joint instability, skin fragility, hypermobility, repeated bruising and ecchymosis, gastroesophageal reflux, hyperacusis. The presence of other familial cases shows the hereditary nature (of the 853 patients, 678 declared a family context related to this disease). In this way, we bring a simple diagnostic tool to effectively contribute to the screening and epidemiology of this disease that many physicians continue to ignore.

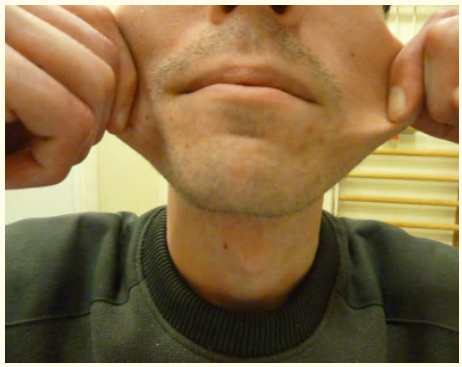

Figure 6: *Hyperetirability of the skin.*

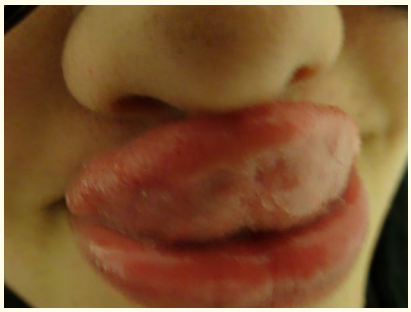

Figure 7: *Gorlin sign, touch the nos with the tongue.*

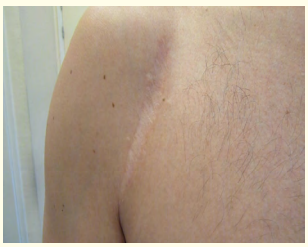

Figure 8: *Pathological scarring.*

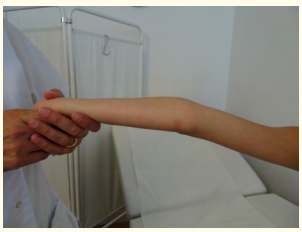

Figure 9: *Hyperlaxity of elbow.*

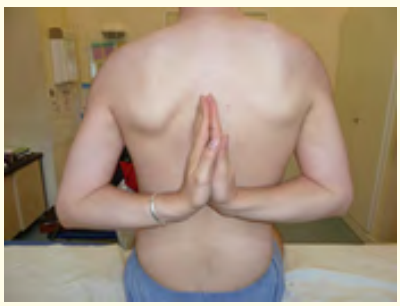

Figure 10: *Hypermobility of Shoulders.*

Figure 11: *Hypermobility of hips and spine.*

Figure 12: *Contracture of knee bending muscles and triceps surae in young boy with EDS.*

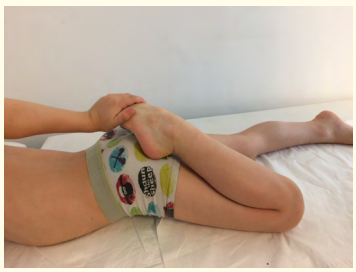

Figure 13: *The same boy without contracture of anterior muscles of lower limb.*

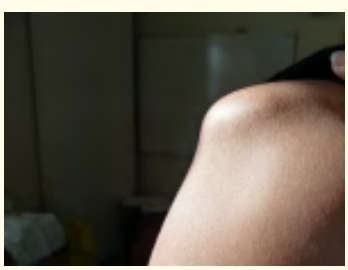

Figure 14: *Dislocation of shoulder.*

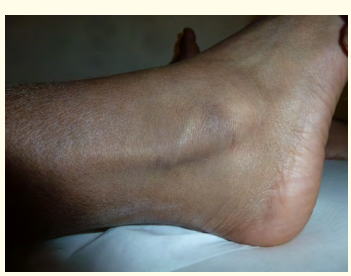

Figure 15: *Tendon luxation of fibularis brevis tendon (instability of ankle).*

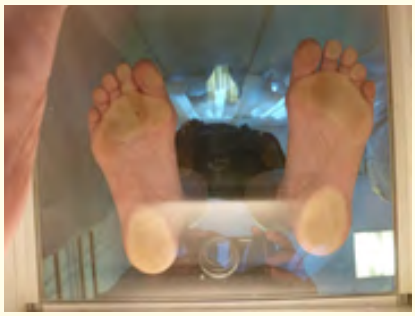

Figure 16: *"Ehlers Danlos foot" flat anterior foot, retractions of middle foot instability of calcaneum in supine.*

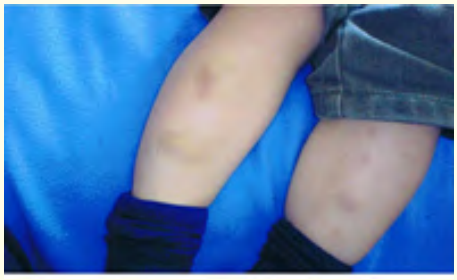

Figure 17: *A child with spontaneous ecchymosis.*

Conclusion

This study shows a homogeneity of symptoms seen in a cohort of 853 patients diagnosed with Ehlers-Danlos syndrome.

The validity of this approach is reinforced by comparison with two control groups (healthy or with another pathology).

Our group of patients is phenotypically stable and homogeneous, which favors a unique type of Ehlers-Danlos disease. It is therefore a clinical tool that is of great interest to geneticists.

We offer a simplified diagnostic tool based on 9 symptoms that allows an easy diagnosis feasible by general practitioners and specialists.

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Conflict of Interest

The authors state that they do not have a conflict of interest.

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