Ehlers-Danlos syndrome (EDS) type III (hypermobile): validation of a somatosensory clinical scale (ECSS-62), involving 626 patients.

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Lecture: French national Academy, Paris 28 février 2017, **PUBLISHED** in ***Bull. Acad. Natle Méd*., 2017, *201*, n°2.**

Translation: Lucette Ducret, MD

Authors declare no conflicts of interest

Reprints: Professor Claude HAMONET.

Article received December 20, 2016, accepted on January 16, 2017

Abstract

It takes a long time before patients are diagnosed with Ehlers-Danlos syndrome (EDS) which is often confused with other pathologies. The absence of genetic test in the common hypermobile manifestation of this hereditary disease (EDS type III) makes it compulsory to base the diagnosis on reliable clinical signs. We propose to introduce a new scale of 62 items to facilitate the diagnosis. A strong correlation link for four groups of symptoms: cutaneous, proprioceptive, dysautonomic and sensory ones, highlighting the homogeneity of this clinical picture. The validity of this grid has been proven by comparing a cohort of 626 EDS patients with 826 unaffected patients and 206 patients consulting for other pathologies.

Keywords : Ehlers-Danlos Syndrome. Joint hypermobility. Joint Instability. Proprioception. Diagnosis. Iatrogeny. Hemorrhage.

INTRODUCTION

At first described by Tschernogobow in Moscow in 1891 and by Ehlers in Copenhagen in 1900, confused by Danlos (Paris, 1908) with elastic pseudoxanthoma, Ehlers-Danlos syndrome is currently diagnosed late (20 years of average delay in our series). It is underdiagnosed despite its high incidence, which can lead to serious complications and put life at risk by ignoring the tissue fragility [1,2]. Incomplete descriptions, a great variety of symptoms linked to the connective tissue ‘s systemic nature, negativity of paraclinical investigations, variability over time, false reputation of benignity make the syndrome look like one of nature's oddities rather than a disease. Resistance to treatment leads the physician astray from the diagnosis. EDS is a pathology which is often unknown to the physician or learned in a split manner. The result is a medical and social exclusion which make Ehlers-Danlos syndrome a huge public health problem. According to the Villefranche classification, Ehlers-Danlos syndrome (EDS) is "one heterogeneous family of several genetic diseases of the connective tissue having in common the triad skin hyperextensibility, joint hyperlaxity and tissue fragility ". Six forms are described. The hyperlaxity that has taken on too much importance in the identification of the syndrome is measured using the Beighton test and defined by a score greater than 4/9 [3]. For certain forms, genetic mutations have been identified. This is the case for mutation Col 3 A1 in the vascular EDS or type IV [4]. In the hypermobile form of Ehlers-Danlos syndrome or Type III, the absence of a biological marker conditions a clinical approach based on heterogeneous criterion sometimes controversial [5]. Besides historical signs, symptomatology appears to be much richer, as put forth by recent years’ publications [6,7]. In the framework of a specific Ehlers-Danlos consultation set up in 1998, we have prospectively studied 626 patients from a cohort of 2,577 people who were diagnosed with hypermobile EDS. We have found that clinical presentation of these patients was characterized, well beyond traditional presentations, by a polymorphic clinical picture associating multiple symptoms (pain, fatigue, proprioceptive, motor, respiratory, digestive, ENT, visual, oral, cognitive, dysautonomic, hemorrhages, ...). Our data is corroborated by those of other teams [8-10]. The cohort observation made it possible to construct a unicist assumption based on a somatosensory system disorder affecting both somatic sensitivity (epicritic, protopathic or proprioceptive), visceral sensitivity and the neurovegetative system, but also visual, auditory, olfactory and vestibular sensorialities. Other authors have also adopted this approach [11, 12]. In the light of this hypothesis, and in support of the systematic clinical observations, a clinical scale was developed in 2005 and finalized in 2014.This clinical observation grid is a semi-directed questionnaire evaluating 79 items (Tables I and II) according to a Likert scale of severity of symptoms. The goal is to define a more complete clinical typology of the disease and identify a stable phenotype.

METHOD

Description of the Ehlers-Danlos syndrome somatosensory clinical scale: (EECS)

Clinical observation of 2,577 patients diagnosed with Ehlers-Danlos hypermobile syndrome have highlighted a large body of symptoms common to most patients. We have constructed an evaluation grid (Tables I and II) comprising 79 clinical events (subjective and objective) that were classified into 16 families: pain, fatigue, sleep, joint disorders and motricity, skin manifestations, dysautonomy, cardiovascular problems, hemorrhagic tendency, digestive and abdominal disorders, bladder sphincter system dysfunction, dental and oral disorders, ENT manifestations, visual disturbances, respiratory symptoms, sexuality and procreation troubles, and cognitive impairment. On the basis of the notion of tissue fragility and sensory integration dysfunction, clinical data have been grouped in 6 axes: 1-fragility of the skin, appendages and teeth, 2-hemorrhagic tendency, 3-sensory and sensorimotor proprioceptive disorders, including respiratory control and sensitivity (pain), 4-dysautonomy including fatigue, digestive and vesico-sphincter disorders, 5- sensory perception disorders (hearing, vision, olfaction, balance vestibular control), 6-cognitive disorders. The evaluation made during a clinical consultation managed by the doctor allows to quantify every symptom and sign of examination according to a Likert scale of severity rated from 0 (Absence) to 4 (very important).

Mathematical modeling of the scale

A weighting coefficient was assigned to each of the 79 clinical manifestations included in the scale. Symptoms 1, 31, 32, 33, 45, 53, 73 and 77 are not assigned to any axis (Tables I and II). The other symptoms are only affected by one axis of the disease. The intensity of an EDS axis is defined as a linear combination of the notes of the composing symptoms:

$$I_{Axe\ i} = \frac{\sum_{j=1}^{16} \sum_{k=1}^{N_j} \delta\left(S_j^k\right) S_j^k \ {}^{i}P_j^k}{\sum_{j=1}^{16} \sum_{k=1}^{N_j} \delta\left(S_j^k\right) \ {}^{i}P_j^k}$$

Equation 1

Where: $I_{Axe\ i}$ is the severity index of Axis i; N_j is the number of symptoms of family j; ${}^{i}P^{k}_{j}$ is the weighting of the symptom k of the famsily j in the Axis i; S^k_j is the note of the symptom k of the family j; S^k_j is 0, 1, 2, 3 or 4 if the symptom is noted or N/A if the symptom is not noted; $\delta(S^k_j)$ worth 0 if the symptom k of the family j is not noted and 1 if it is noted.

With this definition, the severity index of Axis i is a number between 0 and 4.

Description of the Study Controls

To validate the clinical scale, we performed a cross-sectional case-control study comparing 626 patients followed for the hypermobile form of EDS (EDS group), a group of 826 controls (Control group) and a group of 206 patients, followed in primary care, by a physician (GP or specialist) General or specialty group (GPS group), for another pathology than the Ehlers-Danlos. The healthy controls came from a cohort of 3,528 employees in the tertiary sector, followed in systematic consultation of occupational medicine.

Demographic data

In the EDS group, mean age is 32.7 ± 16.99; It comprises 124 men and 502 Women (W/M ratio: 4.1). The extreme ages are 2 years and 72 years. In the control group, mean age is 31.4 years ± 8.27; It includes 408 men and 418 women (ratio W/M: 1.02). Extremes ages are 20 years and 62 years. In the GPS group, mean age was 55.3 years ± 15.95; It includes 109 men and 97 women (W/M ratio: 0.89). The extreme ages are 5 years and 92 years.

RESULTS

Using Equation 1 and the weighting factors in Tables I and II, it is possible to calculate for each patient, the pathology's severity index along each axis. Statistical analysis shows that the distributions of the severity indices on axes 1, 3, 4 and 5 are similar. Values of the severity indices of axes 1, 3, 4 and 5 are correlated two by two. These observations are corroborated by the principal component analysis of axes 1, 3, 4 and 5 which shows that the first eigenvalue is greater than 3 indicating the presence of a dominant mode. Axes 2 and 6 are not correlated. The lack of correlation is explained by the difficulty of appreciating the scores of hemorrhage or cognitive impairment which require more complete clinical analysis. Indeed, the Likert scale is poorly adapted to the quantification of clinical manifestations as these two axes regroup. The mathematical modeling of our scale (Equation 1 and weighting factors (Tables I and II) allows us to calculate for each patient his index of severity according to each axis.

Construction of criteria of typicality and intensity

Axes 1, 3, 4 and 5 are correlated in patients with EDS and, logically, of people who do not have EDS. It is therefore a characteristic correlation of the group of EDS patients. They define a space in 4 dimensions whose geometrical properties can be used to introduce at the same time a measure of the typicality and the measure of the severity of the disease. Any patient can associate a point P in this 4-dimensional space whose coordinates ($x = I_{Axe\ 1}$, $y = I_{Axe\ 3}$, $z = I_{Axe\ 4}$, $t = I_{Axe\ 5}$) are its severity indices on the axes 1, 3, 4 and 5. Obviously, the origin point (0, 0, 0, 0) represents the perfectly healthy subject. The analysis in main components showed that a mode dominated which justifies realizing a linear regression in this space in 4 dimensions from the set of 626 cases. By hypothesis, this straight line should go through the origin point (perfectly healthy patient). This line can be interpreted as the straight line of the typical EDS.

This line which passes through the origin is defined by its vector unit director u:

$$U = (0.522, 0.486, 0.515, 0.475)$$

For a given patient, P, the severity index is defined as the scalar product of the OP vector by the vector u:

$$I_{EDS} = OP \cdot u$$

This index of severity varies between 0 and 8.

We can then define the distance of this patient to the straight line of the EDS as:

$$d_{EDS} = ||OP - (OP \cdot u)\, u||$$

The results allow to classify the patients of the EDS group according to:

I) Typicality in 3 categories: rich clinical expression ($d_{EDS} < 1$), important ($1 \leq d_{EDS} < 2$) and discrete ($d_{EDS} \geq 2$);

(II) Severity in 4 categories: absence of diagnosis or EDS at the pre-clinical stage ($I_{EDS} < 2$), Average EDS ($2 \leq I_{EDS} < 4$), severe EDS ($4 \leq I_{EDS} < 6$) and very severe EDS ($6 \leq I_{EDS} < 8$).

Comparison of EDS, control and GPS groups

Figure 1 shows how the 626 cases of the study are located, the 826 controls and the 206 GPS patients in the I_{EDS}, d_{EDS} plan. There is a strong dissociation between the positioning of the control and GPS groups and the EDS patient group. We also note the very strong homogeneity of the EDS group. Indeed, by grouping the data of FIG. 1 into three categories, the following distribution (as a percentage of each group) is observed:

1. ($I_{EDS} < 2$): 7.2% of the EDS group, 97.1% of the GPS group and 99.6% of the control group.

2. ($I_{EDS} > 2$ & $d_{EDS} < 2$): 92.5% of the EDS group, 2.9% of the GPS group and 0.4% of the control group.

3. ($I_{EDS} > 2$ & $d_{EDS} > 2$): 0.3% of the EDS group, 0.0% of the GPS group and 0.0% of the control group.

EDS patients evenly spread on the chart. On the other hand, healthy controls and GPS fall below the "diagnostic areas".

DISCUSSION

Our study is the first to clinically explore on such a large scale, an important group of patients diagnosed with hypermobile Ehlers-Danlos syndrome. Its interest lies mainly in its ability to demonstrate the homogeneity of the group of patients studied. It contrasts with the heterogeneity of the clinical expression of the disease. The originality lies in an approach that roots from clinical observation, by assuming that patients who came to consult had a common pathogenic disorder consisting of a connective tissue abnormality. The Evaluation Scale Is built on the hypothesis of a somesthetic disorder integrating as much tactile, thermal and painful sensitivity as well as visceral sensitivity, neurovegetative system and visual, auditory, olfactory and vestibular sensorialities. We find that only 2 axes out of 6 (hemorrhagic tendency and cognitive disorders) are not correlated. These results tend to suggest that these two axes should be explored in greater depth and more precise parallel evaluations, particularly at the cognitive level. We chiefly notice that 92.8% of patients in the EDS group were ($I_{EDS} > 2$) in the pathological zone versus 0.4% of the control group and 2.9% of the GPS group. Only 7.2% of patients in the EDS group can be considered as false positives (or at a subclinical stage). Of these 45 cases, 32 were received in a family consultation, 8 have an I_{EDS} severity index greater than 1.5. 5 "false positives" remain (no family history and low severity index) or 0.8% of the cohort. Three witnesses could be considered "false negatives" (or non-detected). These characteristics make it a very interesting tool for the clinician. We notice that our scale has characteristics close to the Brighton criteria proposed by Grahame [7] which give an important place to articular hypermobility. However, this author and Tinkle [13] think that there is an abusive distinction between joint hypermobility syndrome and Hypermobile Ehlers-Danlos syndrome. This distinction disappears if we take a somatosensory approach that allows for a more holistic clinical approach. In the control group, it can be noted that 4.1% (2.2% of men and 5.5% of women) of the population have a Beighton score above 4. Nevertheless, according to ECSS-62, only 0.4% of the general population suffering from EDS is detected hence a prevalence 10 times lower. This confirms the usefulness of the approach in the assessment of EDS hypermobile type whom bibliographic data confirm its heterogeneous clinical character, highlighting its multisystemic character, affecting digestive system [14], proprioception [11,12,] and neurovegetative system [15]. Our data confirm the polymorphic aspect of the symptomatology and underscore a correlation between symptoms. This leads us to conclude that our population is homogeneous. The association of digestive, proprioceptive or vegetative manifestations Is not random. This is a new development which must make it possible to reconsider the concept of hypermobile EDS and to broaden it.

CONCLUSION

This study revealed the homogeneity of the symptoms observed in a cohort of 626 patients diagnosed with Ehlers-Danlos type III syndrome. Finding a correlation between 4 groups of symptoms, classified according to a physiopathological hypothesis (fragility, proprioceptive disorders) makes it possible to assert that the investigated patients belong to the group Ehlers-Danlos syndrome patients. Its validity is reinforced by the comparison with two control groups (healthy or otherwise). 62 items are retained (8 for axis 1, 20 for Axis 3, 25 for axis 4 and 9 for axis 5). We suggest the name of Clinical and somatosensory of EDS scale (ECSS-62). The boundaries between EDS patients ($I_{EDS} > 2$) and unaffected people ($I_{EDS} < 1$) remain to be determined, precisely. This boundary will be a function of Intensity and typicity. This research is an important step. Clinical medicine must, beyond the cognitive, enrich behavioral and psycho-affective aspects. This scale confirms that our patient group is phenotypically stable and homogeneous. This clinical tool could be of interest for future genetic approaches, including genome wide association studies (GWAS) on this population of patients.

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Table I: List of symptoms and weightings along the axes (part 1 of the family "Pain" to the family "Hemorrhagic tendency")

Family	Name	N°	Axis 1	Axis 2	Axis 3	Axis 4	Axis 5	Axis 6
Pains	Overall assessment	1	-	-	-	-	-	-
	Articular or periarticular	2	-	-	1,26	-	-	-
	Muscular, cramps	3	-	-	1,50	-	-	-
	Abdominal	4	-	-	-	1,00	-	-
	Genital	5	-	-	-	1,69	-	-
	Thoracic cage	6	-	-	1,51	-	-	-
	Skin Hyperesthesia	7	2,10	-	-	-	-	-
	Migraines	8	-	-	-	1,62	-	-
Fatigue		9	-	-	-	3,00	-	-
Sleeping disorders		10	-	-	2,33	-	-	-
Articular & motor disorders	Joint hypermobility	11	-	-	1,00	-	-	-
	Hamstrings retraction	12	-	-	1,37	-	-	-
	Sprains or pseudo-sprains	13	-	-	1,00	-	-	-
	Subluxations / dislocations	14	-	-	1,42	-	-	-
	Proprioceptive disorders	15	-	-	1,24	-	-	-
	Scoliosis	16	-	-	3,00	-	-	-
	Plantar retractions	17	-	-	1,83	-	-	-
	Dystonia	18	-	-	2,47	-	-	-
Cutaneous manifestations	Skin's thinness and transparency	19	2,45	-	-	-	-	-
	Difficult healing process	20	1,37	-	-	-	-	-
	Stretch marks	21	1,08	-	-	-	-	-
	Hyperetirability	22	1,27	-	-	-	-	-
Dysautonomia	Feeling cold	23	-	-	-	1,52	-	-
	Intolerance to heat	24	-	-	-	1,83	-	-
	Unexplained fevers	25	-	-	-	1,00	-	-
	Profuse sweating	26	-	-	-	1,00	-	-
	Dry mouth	27	-	-	-	3,00	-	-
	Tachycardia	28	-	-	-	3,00	-	-
	Hypotension	29	-	-	-	1,94	-	-
	Vascular disorders of the extremities	30	-	-	-	2,21	-	-
Cardio-vascular disorders	Morphocardiac modification	31	-	-	-	-	-	-
	Alterations in the arteries	32	-	-	-	-	-	-
	Venous ectasias	33	-	-	-	-	-	-
Hemorrhagic tendency	Dermal hemorrhage	34	-	3,00	-	-	-	-
	Epistaxis	35	-	3,00	-	-	-	-
	Bleeding gums	36	-	3,00	-	-	-	-
	Genital hemorrhage	37	-	3,00	-	-	-	-

Table II: List of symptoms and weightings along the axes (part 2 of the family "Digestive and abdominal disorders" to the family "Cognitive disorders")

Family	Name	N°	Axis 1	Axis 2	Axis 3	Axis 4	Axis 5	Axis 6
Digestives disturbances & abdominal problems	Constipation	38	-	-	-	1,00	-	-
	Bloating	39	-	-	-	1,08	-	-
	Aspirations	40	-	-	-	2,11	-	-
	Dysphagia	41	-	-	-	1,00	-	-
	Gallstones	42	-	-	-	1,00	-	-
	Gastroesophageal reflux	43	-	-	-	2,25	-	-
	Abdominal wall hernia	44	-	-	3,00	-	-	-
Bladder-sphincter dysfunctions	Serious surgical complications	45	-	-	-	-	-	-
	Decreased or lost bladder control	46	-	-	-	2,82	-	-
	Incontinence & urgency	47	-	-	-	2,43	-	-
	Prolapse	48	-	-	1,00	-	-	-
	Urinary infections	49	-	-	-	1,65	-	-
Dental and oral disorders	Temporomandibular	50	-	-	3,00	-	-	-
	Teeth	51	1,81	-	-	-	-	-
	Gums & 0ral mucosa	52	1,32	-	-	-	-	-
	Orthodontics	53	-	-	-	-	-	-
E.N.T. problems	Hyperacusis	54	-	-	-	-	2,10	-
	Hearing loss	55	-	-	-	-	3,00	-
	Tinnitus	56	-	-	-	-	1,61	-
	Hyperosmia	57	-	-	-	-	1,57	-
	Dizziness	58	-	-	-	-	2,66	-
Visual Troubles	Myopia	59	-	-	-	-	1,41	-
	Astigmatism	60	-	-	-	-	1,92	-
	Visual strain	61	-	-	-	-	2,64	-
	Diplopia	62	-	-	-	-	1,00	-
	Conjunctival dryness	63	1,50	-	-	-	-	-
Respiratory disorders	Freeze	64	-	-	2,27	-	-	-
	Breathlessness	65	-	-	1,74	-	-	-
	Recurrent bronchitis	66	-	-	1,00	-	-	-
	Upper respiratory disease	67	-	-	1,00	-	-	-
	Dysphonia	68	-	-	2,42	-	-	-
Sexuality & procreative health	Dyspareunia	69	-	-	-	1,17	-	-
	Erectile problems	70	-	-	-	1,00	-	-
	Conception, delivery	71	-	-	-	1,23	-	-
	Spontaneous abortions	72	-	-	-	1,45	-	-
	Heavy menstrual bleeding	73	-	-	-	-	-	-
Cognitive impairments	Working memory	74	-	-	-	-	-	3,00
	Attention	75	-	-	-	-	-	3,00
	Concentration	76	-	-	-	-	-	3,00
	Executive functions organisation	77	-	-	-	-	-	-
	Spatial orientation	78	-	-	-	-	-	3,00
	Time orientation	79	-	-	-	-	-	3,00

Figure 1: Mapping of the 3 groups (EDS, controls, GPS) according to the severity and the distance to the EDS axis