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Cardiovascular manifestations in the Ehlers-Danlos syndrome hypermobile type

Manifestaciones cardiovasculares en el síndrome de Ehlers-Danlos tipo hipermóvil

Hugo Villarroel-Ábrego[1,a,*]

Abstract

Introduction
In the hypermobile Ehlers-Danlos syndrome (EDSht) there is an important frequency of cardiovascular symptoms. Studies have been conducted in patients diagnosed with Brighton criteria. The objective of this research was to determine the frequency of echocardiographic symptoms and abnormalities in the unselected adult population, diagnosed with EDSht, in a cardiology office, with the criteria of the International Classification of Ehlers-Danlos syndromes, published in 2017.
Methods
The descriptive study in patients diagnosed with EDSht was employed, older than 12 years, attended in an outpatient clinic of cardiology of San Salvador, El Salvador, between 2012 and 2019. Clinical history, physical examination, anthropometry, the Beighton score was employed, 10-minute postural test and echocardiography (ECHO) findings were recorded.
Results
The EDSht was diagnosed in 57 patients, 9: 1 ratio between genders, female predominance; average age was 32.3 + 12.8 years. ECHO was performed in 93% of subjects. The most reported symptom was palpitations (75.4%), but cardiovascular symptoms (chest pain, dyspnea, palpitations, presyncope or syncope) were found in 91.2% of cases. The Dysautonomia (POTS and/or hypotension/orthostatic intolerance) was present in 53.6% of patients. Mitral prolapse had a frequency of 13.2%, valvular myxomatous changes in 17% of cases. An abnormal aortic Z score was infrequent (4 of 53 patients, 7.5%). The echocardiogram showed at least one abnormality in the 26.4% of subjects.
Conclusion
In the EDSht, a high frequency of cardiac symptoms, dysautonomia and abnormal ECHO is recorded. The search for cardiovascular abnormalities when diagnosing EDSht is justified; reciprocally, in young patients with cardiovascular manifestations it is convenient to consider the diagnosis of EDSht.

Keyword: Ehlers-Danlos syndrome, primary dyssautonomy, mitral valve prolapse. (Fuente: DeCS de Bireme).

Resumen

Introducción.
En el síndrome de Ehlers-Danlos hipermóvil (SED_{HT}) hay importante frecuencia de síntomas cardiovasculares, los estudios se han realizado en pacientes diagnosticados con criterios de Brighton. El objetivo de esta investigación fue determinar la frecuencia de síntomas y anomalías ecocardiográficas en población adulta no seleccionada, diagnosticada de SED_{HT}, en un consultorio de cardiología, con los criterios de la Clasificación Internacional de los síndromes de Ehlers-Danlos (CI), publicada el 2017.
Métodos.
Estudio descriptivo en pacientes diagnosticados de SED_{HT}, mayores de 12 años, atendidos en consultorio externo de cardiología de San Salvador, El Salvador, entre 2012 y 2019. Se valoraron historia clínica, examen físico, antropometría, score de Beighton, test postural de 10 minutos y ecocardiografía (ECO).
Resultados.
Se diagnosticó SED_{HT} en 57 pacientes, relación de 9:1 entre géneros, predominio femenino; edad promedio 32,3+12,8 años. Se hizo ECO en 93% de sujetos. El síntoma más reportado fue palpitaciones (75,4%), pero había algún síntoma cardiovascular (dolor torácico, disnea, palpitaciones, presíncope o síncope) en 91,2% de casos. Disautonomía (POTS y/o hipotensión/intolerancia ortostática) estaba presentes en 53,6% de pacientes. El prolapso mitral tuvo frecuencia de 13,2%, cambios mixomatosos valvulares en 17% de casos. Un Z score aórtico anormal fue poco frecuente (4 de 53 pacientes, 7,5%). El ecocardiograma mostró al menos una anormalidad en el 26,4% de sujetos.
Conclusión.
En el SED_{HT} se registra alta frecuencia de síntomas cardíacos, disautonomía y ECO anormal. Se justifica buscar anomalías cardiovasculares cuando se haga diagnóstico de SED_{HT}; recíprocamente, en pacientes jóvenes con manifestaciones cardiovasculares es conveniente pensar en SED_{HT}.

Palabras clave: síndrome de Ehlers-Danlos, disautonomías primarias, prolapso de la válvula mitral (Fuente: DeCS de Bireme).

[1]Faculty of Medicine, "Alberto Masferrer" Salvadoreña University (USAM), Diagnostico Escalon Hospital, San Salvador, El Salvador.

[a]Cardiologist

ORCID:
[*]https://orcid.org/0000-0003-1030-9717

Corresponding author:
Dr. Hugo Villarroel Ábrego

Address: Villavicencio Plaza, segundo Nivel No. 12, Paseo General Escalón y 99 Av Norte, San Salvador, El Salvador, Centro América.

Email: h_villarroel@yahoo.com

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Introducción

The hereditary connective tissue diseases are considered by many doctors to be clinical rarities. However, the joint hypermobility syndrome, better called hypermobile type Ehlers-Danlos syndrome (EDS_{HT}, formerly type III) is the least rare of hereditary collagen diseases; As collagen is abnormal, the resistance and integrity of the skin, joints and other tissues are reduced, giving characteristic phenotypic manifestations (1) (**Figure 1**). Morphological and cardiovascular functional disorders have been frequently documented in patients with inheritable connective tissue diseases. Marfan, Shprintzen-Goldberg, Loeys-Dietz, and Ehlers-Danlos vascular (or type IV) syndromes are associated with severe large vessel aortic injuries, including aneurysms, dissections, and ruptures. (2) In type I osteogenesis imperfecta, has also found an association with sensorineural deafness and aortic anuloectasia, van der Hoeve

syndrome (3). In contrast, the classic (formerly types I and II) and hypermobile types of Ehlers-Danlos syndrome (EDS_{HT}, formerly type III) are not linked to life-threatening vascular lesions. However, reports from all over the world confirm that, in these patients, a series of variables that we will hereinafter refer to as "cardiovascular manifestations" are common: dysautonomia with orthostatic intolerance (postural hypotension, orthostatic postural tachycardia syndrome [POTS], neurally mediated syncope), non-angina chest pain, palpitations, and mitral valve abnormalities (An-VM). (4,5,6,7) It is highly probable that a significant but unknown percentage of all cases of orthostatic intolerance, non-angina chest pain and / or palpitations in young patients may be based on an EDDSS. The true prevalence of EDS_{HT} in the general population is unknown because massive underreporting of cases is suspected (8). As there is no conclusive information in this regard and the available publications are not based on cases derived from cardiology offices, it is important to explore how frequently such cases appear in the cardiology consultation, looking for them prospectively. The specific objective is to quantify the frequency of cardiovascular manifestations in patients with a confirmed diagnosis of hypermobile Ehlers-Danlos syndrome.

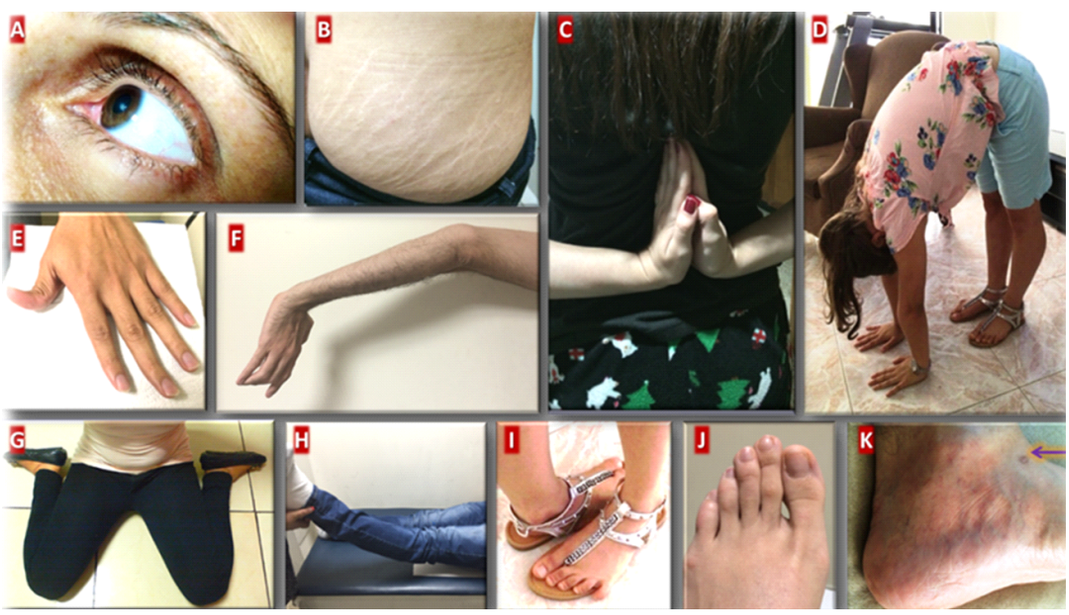

Figure 1. Images of patients affected with the EDSHT. A: blue sclera. B: skin striae. C: Inverted "namasté" sign. D: hands on the floor. E: arachnodactyly. F: Hyperextension of elbows. G: sit in "W". H: Genu recurvatum. G: I: Hyperrotated feet, note the laxity of the toes. J: Ear arachnodactyly, Egyptian foot. K: Flat foot, varicosities, abnormal scarring.

Materials and methods

The objective of this observational research, of case series, with prospective recruitment was to define the frequency of cardiovascular conditions in patients with EDS_{HT} in the cardiology outpatient clinic of the Cardiovascular Center of the Escalon Diagnostic Hospital, San Salvador, El Salvador.

The following clinical elements were assessed:

The Dyspnea frequency at rest, without proven bronchopulmonary or cardiac cause; frequency of non-angina chest pain, as a recurring symptom; frequency of recurring palpitations that do not have a physiological or appropriate cause (exercise, emotion, fever and dehydration, for example). The frequency of orthostatic intolerance (symptoms with sudden orthostatic, symptoms after prolonged orthostatic); postural (orthostatic) hypotension frequency; orthostatic postural tachycardia syndrome (POTS) frequency; frequency of An-VM: thickening, hypermobility and / or prolapse of one or both mitral valve leaflets; Z score value of the aortic root at the sinus level of Valsalva.

The collection of cases began on January 1, 2013 and it was decided that the last case to report would be the deadline on December 31, 2019. All cases diagnosed with Brighton criteria (before 2017) were summoned to the office for clinical reevaluation and eventual reclassification.

Table 1.
Diagnostic Criteria for Ehlers-Danlos Syndrome hypermobile type
Adapted from *The 2017 International Classification of the Ehlers-Danlos Syndromes.*

CRITERION 1:

Generalized joint hypermobility

I. Beighton Score
Total score: _____.

II. 5-point questionnaire

1. ¿ Can you (or ever could) put your hands on the floor without bending your knees?
2. ¿ Can you (or ever could) bend your thumbs up to touch your forearm?
3. ¿ As a child did you like to contort your body in a strange way or could you do the "split"?
4. ¿ As a child or teenager your shoulder or kneecap was dislocated more than once?
5. ¿ Do you consider yourself hypermobile or very flexible or elastic?

¿ THE PATIENT HAS GENERALIZED ARTICULAR HYPERMOVILITY?

Yes □ No□

CRITERION 2:

Two or more of the three groups of characteristics typified as A, B and C
(A+B, A+C, B+C O A+B+C)

Characteristics A:

Systemic manifestations of a more generalized connective tissue disorder. At least 5 conditions must be present:

- Unusually soft and / or velvety skin.
- Mild skin hyperextensibility (> 1.5 cm).
- Unexplained skin striae.
- Piezogenic papules on heels.
- Multiple or recurrent abdominal hernias.
- Atrophic scars in at least two sites without papiraceous or hemosiderotic appearance.
- Pelvic, rectal and / or uterine floor prolapse with no history of predisposing factors.
- Dental crowding and / or vaulted / narrow palate.
- Arachnodactyly: bilateral positive Steinberg (wrist) sign and / or bilateral positive (thumb) Walker sign.
- Stroke / height ratio $\geq$ 1.05
- Mitral valves prolapse.
- Dilation of aortic root with Z-score > +2.

Characteristics B: Positive family history in first-degree relatives who independently meet the criteria for EDS_{HT}.

Characteristics C: At least one (1) of the following requirements must be met:

- Musculoskeletal pain in two or more limbs with daily recurrence for at least 3 months.
- Generalized chronic pain for more than 3 months.
- Recurrent joint dislocation or frank joint instability in the absence of trauma:

a. Three or more atraumatic dislocations at the same joint or two atraumatic dislocations at two different joints at different times.
b. Medical confirmation of instability of at least two joints, in the absence of trauma.

CRITERION 3:

All of the following conditions must be met:

- Absence of excessive skin fragility that leads to suspicion of other variants of the EDS.
- Exclusion of other acquired or inheritable connective tissue diseases, including autoimmune rheumatic conditions.
- Exclusion of alternative diagnoses that may include hypermobility due to hypotonia and / or connective tissue laxity.

Diagnosis of hypermobile Ehlers-Danlos syndrome (EDSh):

□ Positive □ Negative

Inclusion criteria

All cases met three inclusion criteria:

- Consultant in general cardiology clinic.
- Age over 12 years.
- Ehlers-Danlos syndrome, hypermobile type confirmed with the criteria of the 2017 International Classification (see Table 1) (9).

Exclusion criteria

- The presumptive or confirmed diagnosis of hypo / hyperthyroidism without adequate control (TSH should be within the range of 0.47 to 4.64 µIU / ml).
- Hypopituitarism.
- Adrenal pathology or history of adrenalectomy.
- Shy-Drager syndrome.
- Diabetic neuropathy with dysautonomia.
- Uncontrolled hypertension according to the goals proposed by the 2017 guidelines of the American College of Cardiology and the American Heart Association (AHA).
- Structural heart disease: left ventricular hypertrophy, ischemic necrosis, systolic or diastolic dysfunction of the left ventricle, hypertrophic cardiomyopathy, dilated, restrictive, arrhythmogenic dysplasia of the right ventricle or lack of ventricular compaction; Patients who have suffered rheumatic heart disease, Chagas disease or perimyocarditis of any etiology will also be excluded.
- Subclinical coronary artery disease or as demonstrated by imaging studies.
- Patients with conditions that may generate secondary cardiac valve damage: use of anorectics, illicit intravenous drugs, carcinoid syndrome, antiphospholipid syndrome, autoimmune diseases of collagen.

Any patient case that met at least one of the exclusion criteria was registered to be part of a database, for monitoring purposes, but was not included in the final analysis of the present research.

Procedures

Once the patient with a confirmed diagnosis of EDS_{HT} was identified, a complete medical history, system review and a comprehensive physical examination were systematically carried out. All the information was incorporated into a data collection instrument. The clinical evaluation should be exhaustive regarding date of birth, age, sex, and symptoms of the cardiovascular system, with an emphasis on dyspnea at rest, palpitations, orthostatic intolerance, near-syncope, syncope, and chest pain.

Subsequently, blood pressure (BP) was measured with a wall aneroid sphygmomanometer (Welch-Allyn 767) in a sitting position. After a 15-minute resting period in dorsal decubitus, an active orthostatic test was performed, with a heart rate and BP check every 2 minutes for 10 minutes, under continuous three-channel electrocardiographic monitoring (Norav Medical 1200M, Delray Beach FL, USES). The variables considered were:

- Presence of symptoms associated with orthostatism (not present before the test and relieved by resuming the horizontal position).
- Postural hypotension. Any decrease (orthostatic-induced) in systolic BP greater than or equal to 20 mmHg; and / or a decrease of 10 or more mmHg of diastolic BP.
- Orthostatic Postural Tachycardia (POTS): Increased heart rate from baseline by 30 or more beats per minute, change induced by standing posture and persistent for up to 10 minutes, with rapid reversal upon resuming decubitus.

A standard 12-lead EKG trace was taken (Norav Medical 1200M, Delray Beach FL, USA).

Resting color Doppler echocardiography was indicated in all patients. GE Vivid 3 Pro and GE Vivid 7 equipment (General Electric Company, Fairfield, CT, USA) with 1.7-3.5 MHz multifrequency transducers were used. Each echocardiographic study was exhaustive, but Special emphasis was made on the following variables:

- Aortic root caliber, measured from inner edge to inner edge in diastole, at the level of the Valsalva sinuses, in 2 dimensions on the parasternal long axis; or in M mode, from outer edge to inner edge, according to the recommendations of the American Society of Echocardiography (see Figure 2). Aortic root dimensions were calculated for all patients according to online executable software that corrects the data considering age, sex, and body surface area (available at http://www.marfan.org/dx / zscore).
- Increased thickness (> 5 mm), presence of redundant movement, prolapse of the mitral valve leaflets, mitral valve insufficiency (see Figure 3).

A 3-channel Holter was performed for 24 hours in patients with many palpitations, syncope, or suspicion of inappropriate tachycardia, including QT interval and heart rate variability analyzes in the time and frequency domain (Norav DL800 Holter Recorder , Delray Beach FL, USA). This would clarify the nature of symptoms in some patients, but it was not considered an essential study for the protocol.

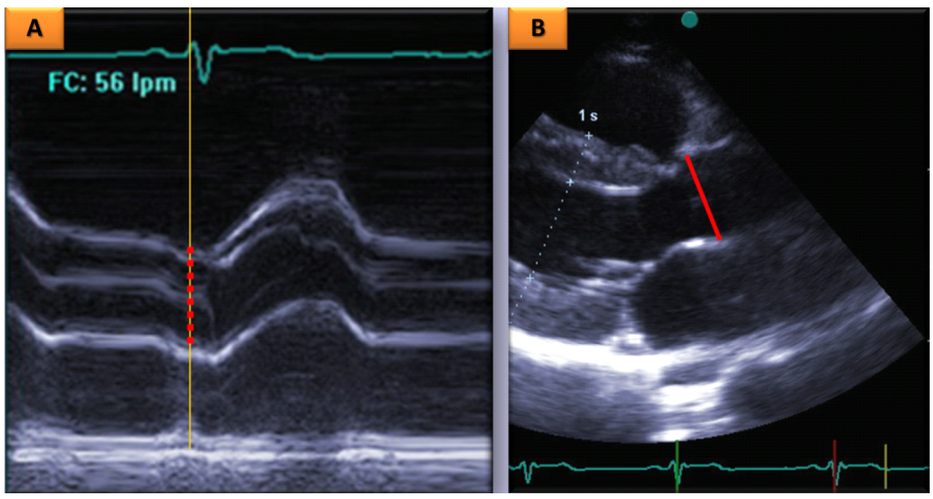

Figure 2: Echocardiography mode M (A) and 2D (B). Techniques for measuring aortic root at the sinus level of Valsalva.

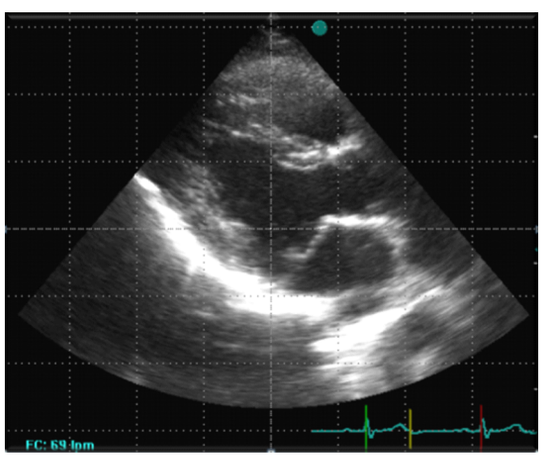

Figure 3: Prolapse of both valves of the mitral valve.

Ethical Considerations

It was explained to all the patients that there would be no data in the publication of the study that would allow their possible identification; the procedures performed are the standard and minimum necessary to confirm the diagnosis, without indication of fasting, venous punctures, taking laboratory tests or invasive procedures outside the office.

Statistical analysis

The frequencies of each of the four cardiovascular conditions in the EDS_{HT} were calculated by dividing the number of cases of each of the conditions by the total number of patients diagnosed with EDS_{HT}, then multiplying the result by 100 to obtain the result in percentage terms. The aortic root Z score of all cases was averaged and reported, with its standard deviation.

Results

After 7 years of prospective search, a total of 158 patients with clinical suspicion of EDS_{HT} were detected based on the traditional Brighton criteria. As the 2017 criteria are much stricter, in most of these patients the diagnosis was ruled out, as had already been evident in a recently published study. (1) After the systematic application of the 2017 International Classification criteria, the final population with confirmed diagnosis was 57 patients, with a high predominance of female patients (n = 52, 91.2%, vs n = 5, 8.8%) with a ratio close to 9: 1. The average age was 32.3 + 12.8 years, with a range between 12 and 59 years (median: 31 years; mode: 25 years). The Table 2 details all the cardiovascular conditions detected and the Table 3 the general characteristics of the population. The frequency of at least one cardiovascular symptom was 91.2% (52 of 57 patients), prevailing inappropriate palpitations and non-angina chest pain. The dysautonomia (orthostatic intolerance / syncope and pre syncope) was frequent in more than half of the patients (53.6%). The Table 4 details the frequency of all symptoms; the manifestations of the dysautonomia are detailed in the Figure 4.

Tabla 2. Inventario de síntomas y condiciones cardiovasculares en pacientes con síndrome de Ehlers-Danlos tipo hipermóvil.

No.	Sexo	Edad (años)	Dolor torácico	Disnea	Palpitaciones	Síncope Presíncope	POTS	Intolerancia ortostática	Hipotensión ortostática	PVM	Mixomatosis mitral	Z score Ao
1	F	14	-	-	-	-	-	-	-			
2	F	27	-	-	+	-	-	-	-	-	-	-1.19
3	F	25	+	+	+	S	+	+	+	-	-	-2.4
4	F	49	-	-	+	-	-	-	-	-	-	-1.71
5	F	40	+	+	+	PS	-	+	-	+	+	-0.04
6	F	35	+	+	+	-	-	+	+	-	+	-2.31
7	F	35	+	+	+	PS/S	+	+	-	-	+	-0.75
8	F	20	+	-	-	-	-	-	-	-	-	-0.11
9	F	15	+	+	+	S	-	-	-	-	-	-0.36
10	F	17	+	-	+	P	+	+	-	-	-	-1.11
11	F	40	+	-	+	-	-	+	-	-	-	-0.42
12	F	20	-	-	-	PS/S	-	+	+	-	-	-0.05
13	F	45	+	+	+	PS/S	-	+	+	-	-	-0.99
14	F	14	-	-	-	-	-	-				
15	F	24	+		+	PS/S	-	+	-	-	-	-0.39
16	F	22	-	-	-	PS/S	-	+	-	-	+	-0.04
17	F	40	-	-	+	-	-	-	-	-	-	2.71
18	M	46	+	-	+	-	-	-	-	-	-	-1.47
19	F	55	-	-	-	-	-	+	-			
20	F	27	-	+	-	-	-	-	+	-	-	-0.3
21	F	21	+	+	+	-	+	+	+	+	+	-0.78
22	F	23	-	-	+	P	+	+	-	-	-	1.35
23	F	42	+	-	+	-	-	-	-	-	-	-0.36
24	F	39	-	+	+	P	-	-	-	-	-	-1.27
25	F	29	-	+	+	-	-	-	-	-	-	-0.54
26	F	51	+	+	+	-	-	+	-	+	+	0.95
27	F	39	+	+	+	P	+	-	-	-	-	-2.13
28	F	53	+	-	+	-	-	-	-	-	-	-1.79
29	F	31	-	-	-	-	-	-	-	-	-	-0.33
30	F	31	-	-	-	S	-	-	-	-	-	-2.24
31	F	19	+	+	+	-	+	+	-	-	-	-0.51
32	F	43	+	-	+	-	-	-	-	+	+	-0.93
33	F	50	+	+	+	P	-	+	-	+	-	-0.05
34	F	51	-	-	-	-	+	-	+	-	-	-1.58
35	M	22	+	-	+	-	+	+	-	-	-	-1.54
36	F	38	+	+	+	S	+	+	+	-	-	0.06
37	F	41	+	-	+	-	-	-	-	-	-	0.12
38	F	59	+	-	-	-	-	-	-	-	-	-0.71
39	F	44	+	-	-	-	-	-	-	-	-	2.81
40	F	38	+	-	+	-	-	+	+			
41	F	13	+	+	+	P/S	+	+	-	-	-	-0.16
42	F	46	+	-	+	-	-	-	-	-	-	0.12
43	M	31	+	-	+	-	-	-	-	-	+	-0.47
44	F	33	+	-	+	-	-	+	+	-	-	-1.44
45	F	19	+	+	+	P/S	-	+	-	-	-	-1.77
46	M	52	+	-	-	S	-	+	+	-	-	0.24
47	F	22	-	-	+	-	-	-	-	-	-	-0.46
48	M	15	+	-	+	P	-	+	-	-	-	2.21
49	F	24	+	+	+	P/S	-	+	+	-	-	-1.32
50	F	25	+	-	+	P/S	+	+	+	-	-	0.26
51	F	24	+	+	+	S	-	-	-	+	+	-0.17
52	F	26	-	-	+	P/S	-	-	-	+	-	2.46
53	F	20	+	+	+	P/S	+	+	+	-	-	-0.45
54	F	12	+	-	-	-	+	+	-	-	-	0.34
55	F	57	+	+	+	P/S	-	-	-	-	-	0.17
56	F	25	-	-	+	-	-	-	-	-	-	0.26
57	F	25	+	-	-	P	-	-	-	-	-	-1.26

Clave. PVM: prolapso valvular mitral; S: síncope; PS: presíncope. Cuadros en gris: No datos disponibles.

Two-dimensional color Doppler ECO was performed in 53 of the 57 recruited patients; in four cases the patients did not keep appointments. In none of these cases was the diagnosis of EDS_{HT} compromised because, even in the absence of the diagnosis of mitral valve prolapse, in each case the minimum number of characteristics of type A required in Criterion 2 (to certify diagnosis) was satisfied.

The ECO showed some anomaly in 26.4% of patients. The prevalence of morphological abnormalities of the mitral valve and / or leaflet prolapse was 20.7% (that of prolapse was 13.2%). Few cases showed any case of Valsalva sinus dilation (7.5%). The detail of the echocardiographic data is graphed in Figure 5.

Table 3
Characteristics of the patient population with EDS_{HT} (n=57)

Female / male gender	91,2%/8,8% (52/5)
Average age	32,3±12,8 years
Body mass index	24,32±4,11 Kg/m^2
Average Beighton score	6,6±1,5 points

Table 4
Frequency of cardiovascular symptoms in the EDS_{HT} (n=57)

Symptom	Frequency (%)
Chest pain	39
Dyspnea at rest	21
Palpitations	43
Near-syncope / syncope	26
Syncope	17
No symptoms	5

Discussion

This research differs from others previously published (10) for the following reasons: The population affected by EDS_{HT} has sought cardiology consultation for the symptoms suffered and not for knowledge that they suffered from an inherited connective tissue disease; exclusively the criteria of the 2017 International Classification have been used, excluding the other patients included within the spectrum of hypermobility; In all cases, an exhaustive evaluation was made by systems, so that medical conditions that could cause cardiac or hemodynamic changes were the cause of exclusion from the study; this is essential for the diagnosis of dysautonomia. Finally, an inventory of clinical complaints and not just echocardiographic findings has been made.

As in a previous research (11), the 9: 1 ratio in terms of female vs. male is confirmed. It is evident that there is a high prevalence of symptoms related to the cardiovascular system. It is important to consider the numerous cases of dysautonomia, a syndromic diagnosis clearly demonstrated with techniques such as monitoring during orthostatism. It has been a constant complaint of most patients, especially female patients, that they attribute their discomfort to hypochondria, anxiety or psychofunctional disorders, with prior visits to multiple clinics of different specialties being common before a definitive diagnosis of EDS_{HT}.

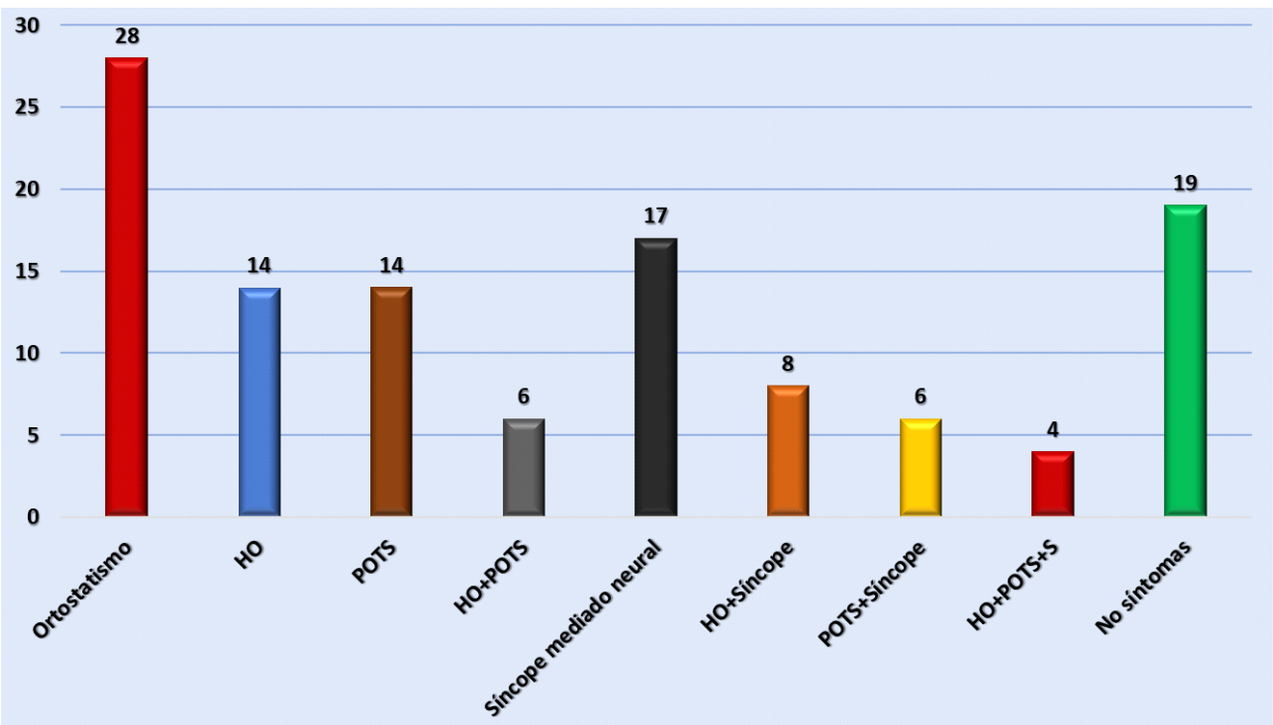

Figure 4: Frequency of symptoms of orthostatic intolerance in the EDSHT (n=56).

Dysautonomia / orthostatic intolerance

The Orthostatic intolerance syndrome has three major clinical manifestations: orthostatic hypotension, neurally mediated syncope, and POTS. (11) According to Ricci et al, the prevalence of orthostatic hypotension is less than 5% in patients younger than 50 years. (11) In our case series, a 14 of 57 subjects met the criteria for orthostatic hypotension, corresponding to a notable 24.6%, so this association seems causal and not accidental. The same thing happens with POTS: one out of every 4 of our patients with EDS_{HT} presents it, something that had been confirmed by Wallman et al (12), who detected EDS_{HT} in 18% of patients with POTS; it is typical that patients present acrocyanosis, venous plethora of the limbs,

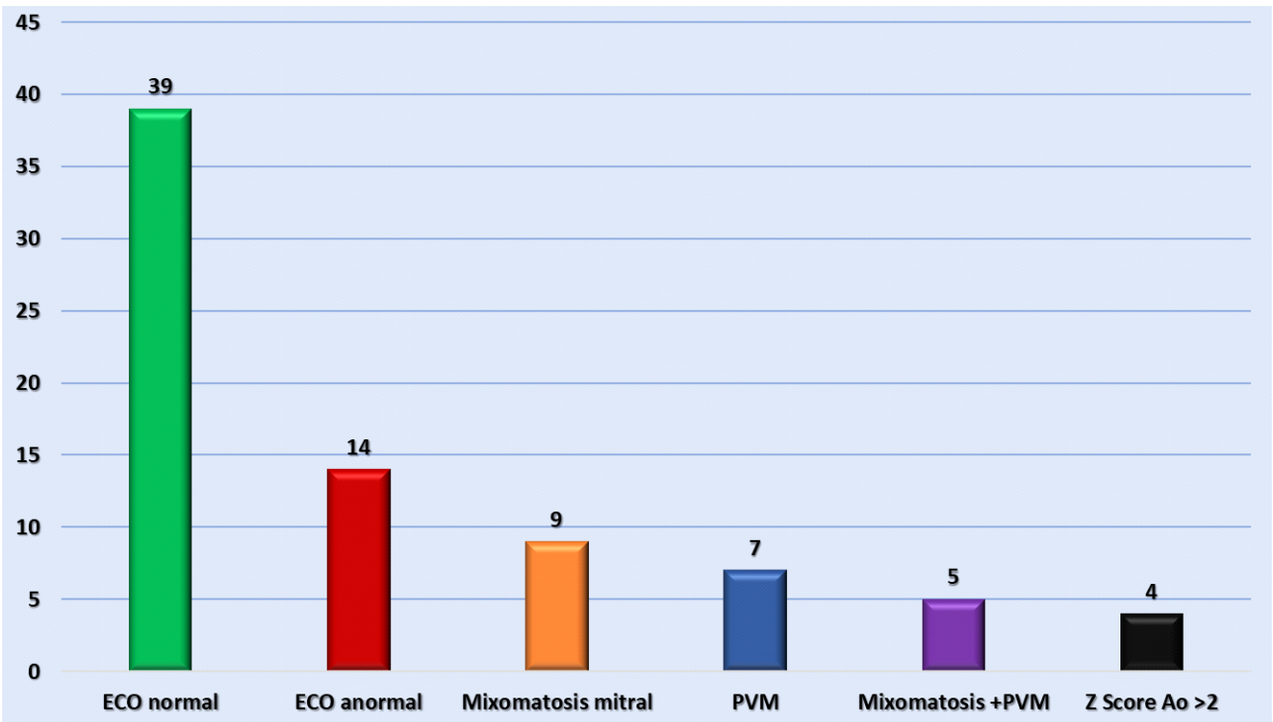

Figura 5: Frecuencia de anomalías ecocardiográficas en el SED_{HT} (n=53).

and considerable discomfort during the standing position, even if only for a few minutes; there was a history of syncope in 8 of 14 patients with POTS of our casuistry, higher than the 30% estimated by Raj et al. (13) As for the syncope and near syncope, causes associated with structural cardiac damage, sustained arrhythmia, valve disease, or drugs, almost half of the patients had experienced these symptoms at least once, a high prevalence for any age group, despite the fact that it is a frequent medical problem especially the neurally mediated one (15% of minors, up to 39% in a survey of medical students). (14)

Myxomatosis / mitral valve prolapse

According to Delling et al, the prevalence of mitral valve prolapse is 2-3% of the general population (6), with or without valve thickening of at least 5 mm. Considered as one of the characteristics A of criterion 2 for the diagnosis of EDS_{HT}, our prevalence of about 13% is not atypical, with myxomatous changes (thickening, hypermobility) without prolapse in another 17%: about a third of patients had structural alterations mitral valve, with or without valve insufficiency, in all cases of mild degree; all prolapse patients were symptomatic. Dolan et al cite a prevalence of only 6% (14), but their study was published in 1997, based on the classic Brighton criteria and not on the demanding ones of the International Classification, so it is not ruled out that in that survey has included many hyperlax who would not have qualified for our research. Although a mutation of filamin A (or actin-binding protein) has been identified as causing an X-linked form of mitral prolapse (6,15), the causal genes for the most common form are inherited in an autosomal pattern dominant have not yet been identified. The Mitral prolapse is an entity that evolves under epigenetic and perhaps environmental influences; in gene carriers involved without morphological abnormalities at an early age, these influences could lead to some non-diagnostic morphological alterations (probably valve thickening and redun-

dancy) until, at later stages, well-defined prolapse occurs, later associated with various degrees of mitral regurgitation.

Aortic root dilation

Levy et al affirm that, when present, aortic root dilation is slight and does not carry a risk of dissection (16), unlike ailments such as Marfan syndrome or the vascular type of Ehlers-Danlos syndrome. Defined as a diameter that exceeds a Z score of 2.0, our cases were only 4 of the 53 studied by ECO, a low frequency, without any patient reaching a value greater than 4 cm, something that is consistent as described.

Conclusions

The EDS_{HT} records a high frequency of cardiac symptoms, dysautonomia, and abnormal echocardiographic findings. This would justify a systematic search for cardiovascular abnormalities when diagnosing EDS_{HT}; conversely, in young patients with cardiovascular, organic or functional manifestations, it is advisable to think about the possibility of a EDS_{HT}. It is convenient to periodically follow up patients with alterations in the morphology of the mitral valve or aortic ring, considering that the phenotype may evolve due to influences not yet well understood.

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