

Refining Patterns of Joint Hypermobility, *Habitus*, and Orthopedic Traits in Joint Hypermobility Syndrome and Ehlers–Danlos Syndrome, Hypermobility Type

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Manuscript Received: 26 April 2016; Manuscript Accepted: 7 December 2016

Joint hypermobility syndrome (JHS) and Ehlers–Danlos syndrome, hypermobility type (EDS–HT) are two overlapping heritable disorders (JHS/EDS–HT) recognized by separated sets of diagnostic criteria and still lack a confirmatory test. This descriptive research was aimed at better characterizing the clinical phenotype of JHS/EDS–HT with focus on available diagnostic criteria, and in order to propose novel features and assessment strategies. One hundred and eighty-nine (163 females, 26 males; age: 2–73 years) patients from two Italian reference centers were investigated for Beighton score, range of motion in 21 additional joints, rate and sites of dislocations and sprains, recurrent soft-tissue injuries, tendon and muscle ruptures, body mass index, arm span/height ratio, wrist and thumb signs, and 12 additional orthopedic features. Rough rates were compared by age, sex, and handedness with a series of parametric and non-parametric tools. Multiple correspondence analysis was carried out for possible co-segregations of features. Beighton score and hypermobility at other joints were influenced by age at diagnosis. Rate and sites of joint instability complications did not vary according to age at diagnosis except for soft-tissue injuries. No major difference was registered by sex and dominant versus non-dominant body side. At multiple correspondence analysis, selected features tend to co-segregate in a dichotomous distribution. Dolichostenomelia and arachnodactyly segregated independently. This study pointed out a more protean musculoskeletal phenotype than previously considered according to available diagnostic criteria for JHS/EDS–HT. Our findings corroborated the need for a re-thinking of JHS/EDS–HT on clinical grounds in order to find better therapeutic and research strategies. © 2017 Wiley Periodicals, Inc.

Key words: Beighton score; diagnostic criteria; dislocations; Ehlers–Danlos syndrome; joint hypermobility; Marfanoid *habitus*

How to Cite this Article:

Morlino S, Dordoni C, Sperduti I, Venturini M, Celletti C, Camerota F, Colombi M, Castori M. 2017. Refining patterns of joint hypermobility, *habitus*, and orthopedic traits in joint hypermobility syndrome and Ehlers–Danlos syndrome, hypermobility type.

Am J Med Genet Part A 173A:914–929.

INTRODUCTION

Joint hypermobility syndrome (JHS) is a still neglected, heritable disorder coupling generalized joint hypermobility (GJH) with variable consequences of joint instability, musculoskeletal pain,

Conflict of Interests: The authors declare that there is no conflict of interest concerning this work.

Grant sponsor: C.E.D.I. Onlus.

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Article first published online in Wiley Online Library (wileyonlinelibrary.com): 7 March 2017

DOI 10.1002/ajmg.a.38106

and subtle skin features [Grahame et al., 2000]. Since the first report of GJH as a recognizable feature and the delineation of the Beighton score (BS [Kirk et al., 1967; Beighton et al., 1973]), our knowledge on the clinical impact of GJH is markedly changed. From the first attempt of defining GJH “benign” because it was originally thought associated with few consequences of a harmless body built or a physical asset, GJH is now increasingly re-interpreted as the “tip of the iceberg” of present or prospective systemic disorders. Among them, JHS is emerging as the most common condition, but its significant overlap with the apparently rarer Ehlers–Danlos syndrome hypermobility type (EDS–HT) inflames the scientific community [Castori and Colombi, 2015]. To date, many researchers and practitioners consider JHS and EDS–HT undistinguishable at the clinical level [Tinkle et al., 2009]. Although we are still waiting for the identification of the molecular basis of JHS and EDS–HT [De Paepe and Malfait, 2012; Mayer et al., 2013], there is increasing evidence for the co-segregation of JHS and EDS–HT as a single trait with variable expressivity in the familial cases (i.e., JHS/EDS–HT) [Tinkle et al., 2009; Castori et al., 2014a].

Different sets of criteria are being used for diagnosing JHS (Brighton) and EDS–HT (Villefranche) [Beighton et al., 1998; Grahame et al., 2000]. Their overlap is notable as both include a high BS, pain, dislocations, and skin changes. However, differences exist concerning the definition of these criteria in the two sets. This probably reflects the different perspectives of the medical communities by whom they were originally delineated (i.e., rheumatologists for JHS, pediatricians and geneticists for EDS–HT) and the different populations in which these two diagnoses are more commonly ascertained (i.e., women for JHS and children for EDS–HT) [Tinkle et al., 2009]. In the last decade, the number of patients attending specialized clinics is increasing with an urgent need for standardizing diagnosis and management [Rombaut et al., 2015a; Palmer et al., 2016]. The original sets of criteria raised from an “opinion”-based approach from the converging experience of a few experts. Conversely, in the last years, many papers refine some of the previously identified pleiotropic features of the syndrome, such as the mucocutaneous and ocular involvement [Gharbiya et al., 2012; Castori et al., 2015], and underline other entirely novel manifestations, such as gastrointestinal involvement and autonomic dysfunction [Zarate et al., 2010; De Wandele et al., 2014]. The role of fatigue and chronic pain is also emphasized in JHS/EDS–HT [Voermans et al., 2010a,b; Voermans and Knoop, 2011]. While many articles offer a global impact of these features in JHS/EDS–HT, the observation of families and heterogeneous patients’ cohorts suggest an age-influenced phenotype [Castori et al., 2010a, 2011, 2013, 2014a, 2015]. Nevertheless, though originally considered relevant features, little attention was put on the extent and evolution of anthropometry, consequences of joint instability and orthopedic traits in JHS/EDS–HT.

This is the first study systematically assessing anthropometry, orthopedic trait and distribution of whole-body joint hypermobility in JHS/EDS–HT. Data were extracted retrospectively from the medical records of 189 JHS/EDS–HT patients evaluated in two Italian expert centers for systemic hereditary connective tissue disorders. Our results could contribute to a better definition of

the physical phenotype of JHS/EDS–HT and to refine its clinical diagnostic criteria for a prompt recognition of the disorder.

PATIENTS AND METHODS

This study was intended as a bi-centric, retrospective research gathering clinical data from two Italian centers for the diagnosis and management of systemic hereditary connective tissue disorders, particularly Ehlers–Danlos syndromes. The center with the highest number of patients lead the study and was considered the training center (TC). Data were then compared with the second center, which was named validation center (VC). All patients gave their informed consent to the study. This study was in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Patients’ Selection and Phenotype Definition

Patients of the TC were selected from the jointed service for joint hypermobility and Ehlers–Danlos syndrome at the Medical Genetics Outpatient Service of the San Camillo–Forlanini Hospital and at the Physical Medicine and Rehabilitation Center of the Policlinico Umberto I University Hospital in Rome. Patients of the VC were enrolled from the Center for the Diagnosis and Management of Ehlers–Danlos syndromes and Hereditary Connective Tissue Disorders at the University of Brescia and Spedali Civili University Hospital in Brescia. All patients underwent a direct clinical evaluation aimed at extensively defining the phenotype and associated management issues. The general assessment followed standard procedures as previously described [Castori et al., 2014a, 2015]. In brief, all patients were evaluated for the available clinical diagnostic criteria for JHS (Brighton criteria) [Grahame et al., 2000] and Ehlers–Danlos syndrome (Villefranche criteria) [Beighton et al., 1998]. When necessary, other sets of criteria for cognate disorders, such as the revised Ghent criteria for Marfan syndrome [Loeys et al., 2010] were also applied. Differential diagnosis included heart ultrasound and ophthalmological survey and, when necessary, bone densitometry and spine and brain MRI, as well as a non-invasive assessment of the vascular tree, according to the recently published Italian diagnostic approach for Ehlers–Danlos syndromes [Castori and Colombi, 2016]. In case of persistent doubts concerning the overlap with other hereditary connective tissue disorders (in particular, vascular and classical EDS, and Loeys–Dietz syndromes), appropriate molecular studies were performed by the national reference laboratory for the molecular diagnosis of EDS and related conditions (Brescia). However, supplementary molecular studies were carried out in a few patients and most cases were limited to the exclusion of point mutations and intragenic rearrangements of *COL5A1* and *COL5A2* as previously stated [Ritelli et al., 2013]. Once excluded partially overlapping hereditary soft connective tissue disorders on clinical grounds and, if considered necessary, by molecular tools, all patients were classified as affected by JHS (Brighton criteria only), EDS–HT (Villefranche criteria for EDS–HT only) or JHS + EDS–HT (Brighton and Villefranche criteria), as previously detailed [Castori et al., 2014a]. Both sets of criteria were strictly applied. The clinical diagnosis of EDS–HT was attributed only in presence of both major criteria, while that of JHS was fixed in presence of both major, one major and two minor, or four minor

criteria [Beighton et al., 1998; Grahame et al., 2000]. As EDS-HT is considered the unique major Ehlers-Danlos syndrome subtype lacking a confirmatory laboratory test [Mayer et al., 2013], diagnosis remained clinical in all patients.

Patients' Evaluation

Age at examination, sex and handedness was registered in all available subjects. GJH was primarily assessed by the BS [Beighton et al., 1973]. This score is composed of five maneuvers: four of them are tested passively on both sides of the body and one is tested actively. BS is a 9-point evaluation with attribution of one point in the presence of any of the following: (a) passive apposition of the thumb to the flexor aspect of the forearm (one point for each hand), (b) passive dorsiflexion of the V finger beyond 90° (one point for each hand), (c) hyperextension of the elbow beyond 10° (one point for each arm), (d) hyperextension of the knees beyond 10° (one point for each leg), (e) forward flexion of the trunk with the knees extended and the palms resting flat on the floor. In non-collaborative subjects (such as, toddlers and adults in wheelchair), the upper end of the sum was reduced by one point by excluding the maneuver for forward flexion of the trunk. In this case, the highest score was 8/8. The 5-point questionnaire was also used as a pre-screening tool [Hakim and Grahame, 2003], but their results were not further used for the present work as this tool was not yet included in any set of diagnostic criteria. Range of motion (ROM) was also assessed for a range of joints and group of joints not included in the BS. As well representative of the entire human body, we selected temporomandibular joint (TMJ) (hypermobile for a full opening of >50 mm), 2nd-4th metacarpophalangeal (MCP) joints (hypermobile with a dorsal passive extension >40°), proximal and distal phalangophalangeal joints at 2nd-4th fingers (hypermobile with a dorsal active extension >0°), metatarsophalangeal (MTP) joint at 1st toe (hypermobile with a dorsal passive extension >70°), hip (hypermobile with an abduction with leg extended >45°), ankle (hypermobile with a passive dorsiflexion >30°), neck in rotation (hypermobile for an active rotation >90° at each side), and lateral flexion (hypermobile for an active lateral flexion >45° at each side), thoracolumbar spine in rotation (hypermobile for a passive rotation >30-45° at each side) and lateral flexion (hypermobile for an active lateral flexion >35° at each side). All standard values for these extra joints were extracted and only slightly adapted from Clarkson [2012] and obtained with the use of an orthopedic goniometer or a flexible tape. Presence of hypermobility (interpreted as a dichotomous feature: yes or not) was registered on both sides.

A set of static orthopedic features were systematically registered at direct examination and included: (fixed) subluxation of the distal ulna, (fixed) subluxation of the first metacarpal bone, *cubitus valgus*, *pectus excavatum*, *pectus carinatum*, dorsal hyperkyphosis (clinical examination), lumbar hyperlordosis (clinical examination), scoliosis (always of mild degree in JHS/EDS-HT $\leq 20^\circ$ at clinical/radiological examination), *genuum valgus*, *hallux valgus*, and in-toeing gait/metatarsus varus. History annotation comprised the site and number of past luxations/subluxations and sprains. Presence of (recurrent) soft-tissue injuries was registered also in presence of three or more episodes. Single or multiple events of tendon and muscle ruptures were also registered. Standard biometry included height (cm), weight (kg), and arm span

(cm), from which the body-mass index (BMI) and arm span/height ratio were calculated. As applied in routine clinical examination, in patients >15 years of age, the presence of leptosomic/ectomorphic and picnic/endomorphous built was established with a BMI <19 and >25, respectively in both sexes. "Dolichostenomelia" was established with an arm span/height ratio >1.03 according to the Brighton criteria [Grahame et al., 2000]. Complementarily, an arm span/height ratio <0.97 was arbitrarily considered indicative for "brachymelia." The presence of wrist and thumb (Steinberg) sign (monolateral or bilateral) was also documented. Data on upper/lower body segment ratio were not available in both groups.

Data from the VC were limited compared to TC and did not include joint mobility measurement outside the BS and selected anthropometric and orthopedic features. ROM was measured with an orthopedic goniometer in the TC only, while the BS was established subjectively. Such a difference was originally established by the senior investigators of the two centers as a result of partially divergent assessment approaches, still in according to available diagnostic criteria. Indeed, both the Vilfranche and Brighton criteria do not explain how to measure ROT for BS score calculation. Recently, a worldwide lack of consensus in the assessment of joint mobility and the diagnosis of JHS/EDS-HT was highlighted by a questionnaire study among European and American experts [Remvig et al., 2014].

Statistical Analysis

A series of descriptive statistics were used to summarize pertinent study information. Chi-square or Fisher's exact test was performed for the comparison of categorical variables. The linear regression model was used to investigate possible relationship between continuous variables. Comparison between the presence/absence of selected features and continuous variables (i.e., age at examination and BS) was performed using the Mann-Whitney non parametric test. All *P* values were reported as 2-sided and *P* values < 0.01 denotes statistically significant association. Multivariate logistic regression analysis considering age, gender, and center was carried out to examine the associations for each feature/or group of features being studied. All analyses were performed by using the SPSS software (SPSS version 21.0, SPSS Inc., Chicago, IL).

Phenotype and evolution of JHS/EDS-HT are extremely variable [Castori, 2012; Castori et al., 2013]. The reasons for such a variability are still obscure, but genetic heterogeneity may be a major contributor. This could also explain as to why the molecular basis of JHS/EDS-HT remains unraveled. The identification of discrete sub-phenotypes seems a good approach to ease the future molecular characterization of JHS/EDS-HT and/or to identify clues for predicting developmental trajectories. For this reason, we further explored our data searching for possible clusters of discrete features within our patients' sample. Multiple correspondence analysis (MCA), which is a descriptive technique designed to analyze simple 2-way and multi-way tables, was considered an adequate tool to evaluate the possible relationship among selected variables and identify specific profiles. Associations between features are represented graphically in the MCA, which is a graphic representation of the statistical relationships between distinct features, whose position in the graphic is exclusively informative

TABLE I. Descriptive Features of the Two Study Groups—Joint Hypermobility and Joint Instability Complications

Feature	Training Center (%)	Validation Center (%)	P-Value
No. of patients			
Females	106 (85.5)	57 (87.7)	0.67
Males	18 (14.5)	8 (12.3)	
Total	124 (100)	65 (100)	
Age (years)			
Median	32	37	0.259 ¹
Range	2–73	5–70	
Total	124	65	
Beighton score			
Median	6.00	4.00	<0.0001 ¹
Range	0–9	0–9	
Total	124	65	
Joint hypermobility, Beighton score			
1st finger right	85 (68.5)	28 (43.1)	0.001
1st finger left	93 (75.0)	31 (47.7)	<0.0001
5th finger right	87 (70.2)	16 (24.6)	<0.0001
5th finger left	96 (77.4)	26 (40.0)	<0.0001
Elbow right	42 (33.9)	38 (58.5)	0.002
Elbow left	60 (48.4)	35 (53.8)	0.48
Knee right	71 (57.3)	18 (27.7)	<0.0001
Knee left	73 (58.9)	22 (33.8)	0.001
Spine	51 (41.5)	37 (56.9)	0.04
Total	124	65	
Joint hypermobility, other sites			
TMJ	46 (37.1)	NA	NA
2nd–4th MCPs right	84 (67.7)	NA	NA
2nd–4th MCPs left	87 (70.2)	NA	NA
2nd–4th PIPs right	40 (32.3)	NA	NA
2nd–4th PIPs left	50 (40.3)	NA	NA
2nd–4th DIPs right	58 (46.8)	NA	NA
2nd–4th DIPs left	61 (49.2)	NA	NA
MTPs right	51 (43.6)	NA	NA
MTPs left	52 (44.4)	NA	NA
Ankle right	32 (27.4)	NA	NA
Ankle left	32 (27.4)	NA	NA
Hip right	49 (41.9)	NA	NA
Hip left	49 (41.9)	NA	NA
Neck rotation right	38 (32.5)	NA	NA
Neck rotation left	35 (29.9)	NA	NA
Neck flexion right	57 (48.7)	NA	NA
Neck flexion left	56 (47.9)	NA	NA
Full spine rotation right	78 (66.7)	NA	NA
Full spine rotation left	78 (66.7)	NA	NA
Full spine flexion right	42 (35.9)	NA	NA
Full spine rotation left	44 (37.6)	NA	NA
Total	118-124		
Dislocations			
1–2	13 (10.5)	7 (10.8)	0.95
3–10	21 (16.9)	13 (20.0)	0.6
>10	42 (33.9)	18 (27.7)	0.39
Habitual/recurrent	8 (6.5)	10 (15.4)	0.05
Fingers	9 (7.3)	4 (6.2)	1.0
Wrists	9 (7.3)	7 (10.8)	0.41
Elbows	9 (7.3)	5 (7.7)	1.0
Shoulders	38 (30.6)	33 (50.8)	0.007
Heels	11 (8.9)	9 (13.8)	0.29
Knees/rotulae	22 (17.7)	13 (20.0)	0.7

(Continued)

TABLE I. (Continued)

Feature	Training Center (%)	Validation Center (%)	P-Value
Hips	31 (25.0)	19 (29.2)	0.53
TMJ	32 (25.8)	28 (43.1)	0.01
Vertebrae	3 (2.4)	2 (3.1)	0.79
Ribs	1 (0.8)	1 (1.5)	1.0
Total	124	65	
Major sprains			
1–2	10 (8.1)	10 (15.4)	0.12
3–10	18 (14.5)	13 (20.0)	0.33
>10	47 (37.9)	21 (32.3)	0.45
Habitual/recurrent	5 (4.0)	6 (9.2)	0.19
Fingers/wrists	12 (9.7)	6 (9.2)	0.92
Elbows	1 (0.6)	1 (1.5)	1.0
Heels	75 (60.5)	38 (58.5)	0.79
Knees	15 (12.1)	17 (26.2)	0.01
Total	124	65	
3 or more soft tissue injuries			
Feature	46 (37.1)	26 (40.0)	0.7
Total	124	65	
Tendon ruptures			
Feature	4 (3.2)	3 (4.6)	0.69
Total	124	65	
Muscle ruptures			
Feature	5 (4.1)	1 (1.5)	0.67
Total	122	65	

Significant *P*-values below 0.01 are indicated in bold.

DIP, distal interphalangeal [joint]; MCP, metacarpophalangeal [joint]; MTP, metatarsophalangeal [joint]; NA, not available; PIP, proximal interphalangeal [joint]; TMJ, temporomandibular joint.

¹Mann-Whitney U test.

[Greenacre, 1984; Lebart et al., 1984]. Features to be analyzed were selected arbitrarily among those which can be easily interpreted as dichotomic and are more representative of what is to date considered the JHS/EDS-HT “core phenotype.”

RESULTS

The TC and VC included 124 and 65 patients, respectively, for a total of 189 individuals from 2 to 73 years of age. Tables I and II summarized rough data obtained in the TC and VC. Groups were comparable for age and sex bias, with the well-known skewed sex ratio due to an excess of affected females (Table I [Castori et al., 2010b]). Significant differences were noted concerning the BS range with a median score of six and four in the TC and VC, respectively. Information on joint instability complications (i.e., dislocations, sprains, soft-tissue injuries, and ruptures) were comparable between groups with a few exceptions, including the number of dislocations at shoulders which were more common in the VC (Table I). Anthropometry and the rate of selected orthopedic traits did not differ between groups (Table II).

Beighton Score (and Age)

In previous ecologic studies, an inverse correlation between BS and age was suggested for Italian patients [Castori et al., 2011, 2014a]. In the present work, correlation between BS and age at diagnosis was further investigated and a statistically significant inverse relationship was confirmed in both groups,

with a linear R square of 0.33 (*P*-value: <0.0001) and 0.17 (*P*-value: 0.001) in the TC and VC, respectively (Fig. 1A). This phenomenon was comparable between the two groups (*P* = 0.38).

In a pilot research on 50 JHS/EDS-HT Italian patients, we found a cut-off of 33 years for the transition from a positive to a negative BS [Castori et al., 2011]. In the present study, the same trend was found in the TC group with a *P*-value of <0.0001, while borderline *P* values were found in the VC (i.e., 0.02; Fig. 1B). Still in accordance with our previous observations [Castori et al., 2011], we evaluated the presence/absence of the single items of the BS by age at examination (Table III). Results were different between groups. In the TC, the mean age was significantly lower among individuals with hypermobility at any single joint compared to those without, except for the right knee and spine. In the VC, all results were comparable between the two groups (i.e., presence and absence).

Hypermobility in Other Joints (and Age)

In the TC, we also evaluated ROM in 21 additional joints or groups of joints outside the five maneuvers of the BS (Table I). Figure 2 compares age at examination and presence/absence (dichotomic trait) of joint hypermobility (i.e., ROM values above normal) for each of these 21 extra joints. Statistically significant values were obtained for all sites, except TMJ, MTP joints (bilateral), ankles (bilateral), and spine (rotation). In these joints, median age, and age range of patients showing (presence) and not showing (absence) hypermobility were comparable, while the median age of

TABLE II. Descriptive Features of the Two Study Groups—Anthropometry, *Habitus* and Orthopedic Traits

Feature	Training Center (%)	Validation Center (%)	P-Value
BMI			
Median	22.25	21.57	0.49 ¹
Range	16.16–35.16	15.24–36.33	
Total	96	57	
Arm span/height ratio			
Median	1.045	NA	NA
Range	0.91–1.073		
Total	121		
Habitus (BMI)			
Leptosomic	15 (15.6)	10 (17.5)	0.76
Picnic	23 (24.0)	13 (22.8)	0.87
Total	96 (100)	57 (100)	
Habitus (arm span)			
Dolichostenomelia	30 (24.8)	NA	NA
Brachymelia	12 (9.9)		
Total	121		
Wrist sign			
Right	26 (21.5)	9 (15.8)	0.37
Left	27 (22.3)	10 (17.5)	0.46
Monolateral	5 (4.1)	7 (12.3)	0.06
Bilateral	24 (19.8)	5 (8.8)	0.06
Total	121	57	
Thumb sign			
Right	11 (9.0)	4 (7.0)	0.78
Left	14 (11.5)	5 (8.8)	0.58
Monolateral	5 (4.1)	3 (5.3)	0.71
Bilateral	10 (8.2)	3 (5.3)	0.76
Total	121	57	
Orthopedic traits			
FDSU right	81 (65.9)	NA	NA
FDSU left	86 (69.4)	NA	NA
1st MCP subluxation right	7 (5.6)	NA	NA
1st MCP subluxation left	5 (4.0)	NA	NA
<i>Pectus carinatum</i>	5 (4.2)	1 (1.5)	0.33
<i>Pectus excavatum</i>	9 (7.5)	9 (13.8)	0.16
Dorsal hyperkyphosis	83 (67.5)	40 (61.5)	0.41
Lumbar hyperlordosis	86 (69.4)	44 (67.7)	0.82
Scoliosis (<20 degrees)	67 (54.0)	39 (60.0)	0.43
Cubitus valgus right	65 (52.4)	34 (52.3)	0.99
Cubitus valgus left	52 (41.9)	28 (43.1)	0.88
Genuum valgus right	61 (49.2)	22 (33.8)	0.04
Genuum valgus left	64 (51.6)	24 (36.9)	0.05
Flexible flatfoot right	72 (58.1)	33 (50.8)	0.34
Flexible flatfoot left	67 (54.0)	32 (49.2)	0.53
In-toeing gait right	10 (8.2)	7 (10.8)	0.56
In-toeing gait left	10 (8.2)	6 (9.2)	0.81
<i>Hallux valgus</i> right	33 (27.0)	26 (40.0)	0.07
<i>Hallux valgus</i> left	35 (28.7)	28 (43.1)	0.05
Total	120–124	65	

BMI, body mass index; FDSU, fixed dorsal subluxation of the distal ulna; MCP, metacarpophalangeal (joint); NA, not available.

¹Mann-Whitney U test.

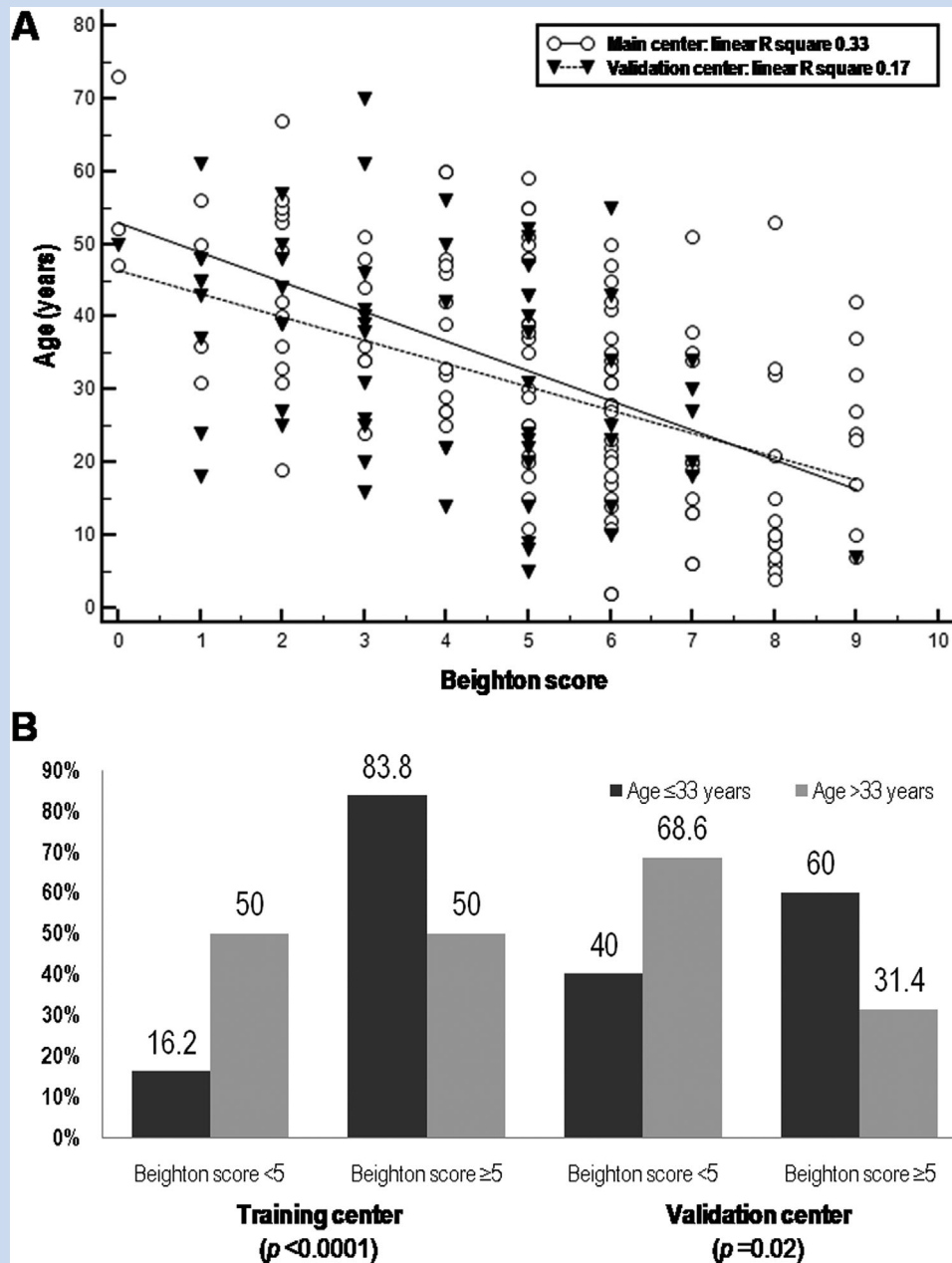


FIG. 1. (A) Scatter plot showing inverse linear correlation between age at examination and Beighton score in the training center (white circles) and validation center (inverse black triangles). In both cohorts an inverse correlation between Beighton score and age was demonstrated. The P -value of the R square was <0.0001 and 0.001 in TC and VC, respectively. (B) Distribution of patients in both groups with or without a positive Beighton score in relation to their age. A dichotomous distribution with a cut-off of 33 years was used according to previous study.

patients presenting the feature was significantly lower than those without in all other joints. We also tried to use these 21 extra sites of joint hypermobility as a tool complementary to BS. We arbitrarily attributed one point to the presence and 0 point to the absence of hypermobility in each joint (or group of joints), similarly to the five maneuvers of the BS. The sum ranged from 0 (i.e., absence of all extra hypermobile joints) to 21 (i.e., presence of all extra hypermobile joints). Comparably to the BS (Fig. 1A), the overall score

diminished according to age at evaluation with a linear R square of 0.33 also for these extra joints (Fig. 3).

Physical Examination and Sex

Differences between sexes concerning somatic manifestations were minimal. Concerning the BS, an excess of hypermobile spine (P -value: 0.007) were noted in women, while borderline P values

TABLE III. Difference in Age for Presence of Specific Beighton Score Items

Beighton score item	Training center			Validation center		
	Presence (years)	Absence (years)	P-Value	Presence (years)	Absence (years)	P-Value
1st finger right						
Mean	25.96	43.31	<0.0001	29.43	37.65	0.026
SD	14.525	12.321		14.315	15.120	
1st finger left						
Mean	27.00	44.68	<0.0001	31.84	36.18	0.193
SD	14.331	13.378		15.771	14.640	
5th finger right						
Mean	26.16	43.78	<0.0001	29.88	35.49	0.223
SD	14.754	11.485		15.213	15.130	
5th finger left						
Mean	27.89	43.54	<0.0001	30.88	36.26	0.166
SD	15.291	12.182		12.959	16.377	
Elbow right						
Mean	24.33	35.05	<0.0001	34.50	33.56	0.826
SD	14.069	15.802		16.688	13.189	
Elbow left						
Mean	26.33	36.19	0.001	30.97	37.77	0.1
SD	14.686	15.835		16.043	13.574	
Knee right						
Mean	28.17	35.77	0.015	26.94	36.85	0.032
SD	16.753	13.957		14.627	14.690	
Knee left						
Mean	28.19	36.04	0.009	27.64	37.42	0.016
SD	16.360	14.429		14.549	14.641	
Spine						
Mean	34.80	29.39	0.048	31.84	37.11	0.107
SD	14.502	16.545		15.833	14.106	

Significant *P*-values below 0.01 are indicated in bold. *P*-values were calculated with the Mann–Whitney U test. Mean and standard deviation are expressed in years. SD, standard deviation.

were noted in males for an excess of hypermobile first (*P*-value: 0.04) and fifth (*P*-value: 0.01) fingers on the right in the TC only. All other BS items were comparable between sexes in both groups. A mean BS value higher in males (6.5) was registered in the TC only. Table IV showed comparison of the other structural features (hypermobility at extra joints, anthropometry and orthopedic traits) between sexes. No differences were noted on anthropometry and only a few significant divergences were registered for the other features. Males resulted more commonly hypermobile than females at neck flexion (both sides), while females showed more frequently *cubitus valgus* on the left.

Joint Instability Complications

In order to test whether age at ascertainment might relate with presence of joint instability complications (i.e., dislocations, sprains, and soft-tissue injuries) at history taking, patients were arbitrarily stratified by age (i.e., ≤20 years, 21–30 years, 31–40 years, >40 years). Sites (dislocations and sprains only) and rate of joint instability complications was evaluated

accordingly (Table V). No major significant difference was registered in term of positive report of previous dislocations and sprains among age categories in both groups. Comparable results were also obtained for sites of dislocations and sprains. A significantly higher rate of soft tissue injuries (three or more events) was registered in adults and elder of the TC only. Tendon and muscle ruptures had a very low rate in both groups and, then, may be considered occasional findings.

Handedness

Patients from the TC were also investigated for a possible role of handedness on the rate of joint hypermobility and bilateral orthopedic traits. No significant difference was observed for fixed subluxation of the distal ulnar epyphysis and 1st metacarpal, *genuum valgus*, *hallux valgus*, *cubitus valgus*, in-toeing gait, flexible flatfoot, and joint hypermobility at knee, elbow, 1st and 5th fingers, 2nd–4th distal and proximal interphalangeal joint of hands, metacarpophalangeal joint, spine (rotation and flexion), neck (rotation and flexion), 1st metatarsophalangeal joint, ankles, and hips.

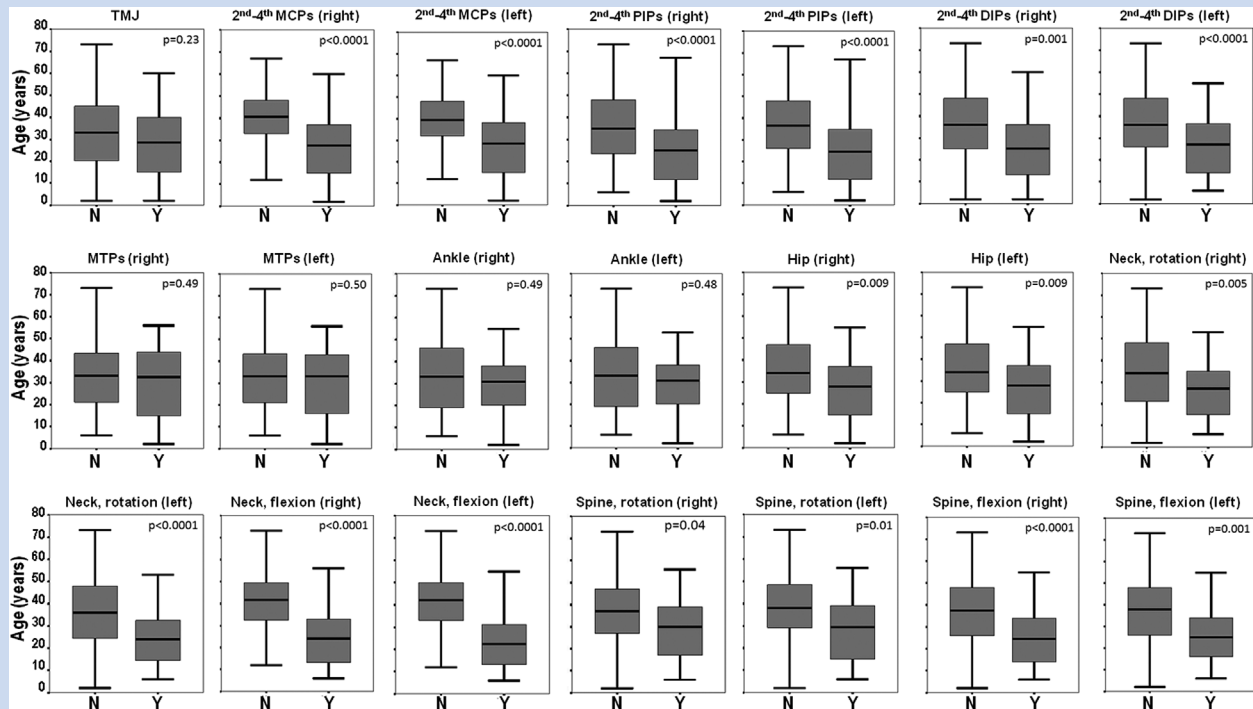


FIG. 2. Box plots comparing the presence [Y = yes] and absence [N = no] of joint hypermobility (i.e., an excessive range of motion) at 21 joints or groups of joints outside the Beighton score in relation with age at examination. The horizontal black line indicates the median value, the upper box the first quartile, the lower box the remaining three quartiles, and the vertical line the entire range of values observed in the patient sample.

Multiple Correspondence Analysis and Multivariate Logistic Regression Analysis

MCA for sex, BS (≥ 5 vs. < 5) and eleven selected orthopedic, and anthropometric traits did not depict a clear-cut clustering of features in discrete physical subphenotypes (Fig. 4). Anyway, low BS, brachymelia, and absence of the selected features (white dots) tend to associate together with a net separation from high BS and presence of orthopedic traits, dolichostenomelia according to the Brighton criteria (arm span/height ratio > 1.03) and arachnodactyly (positive wrist or Steinberg signs—the clinical definition of arachnodactyly in JHS/ED-HT is a matter of debate and it will be probably included in the future diagnostic criteria). Male sex, pectus deformities, positive wrist sign, and flexible flatfoot are the most divergent features. More specifically, positive wrist sign tends to cluster with positive thumb sign, recurrent enthesopathies, and *hallux valgus*; *pectus* deformities segregate with male sex and associate with dolichostenomelia; and flexible flatfoot seems to combine with brachymelia and low BS.

Statistical analyses carried out with an univariate approach was further investigated with a multivariate logistic regression analysis. Positive results (i.e., with a P -value < 0.01) were highlighted in Table VI. Significant influence of sex and evaluation center was also evident at the multivariate logistic regression analysis. Occasional significance was also registered for single orthopedic traits and joint instability complications.

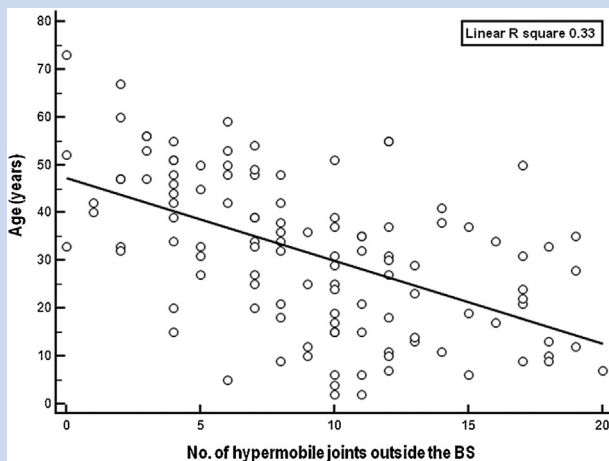


FIG. 3. Scatter plot showing inverse linear correlation between the presence of joint hypermobility at joints or groups of joints (no. 21) outside the Beighton score and age at examination of patients from the TC. For all joints, we attributed 1 point to their presence and 0 points to their absence for a maximum total of 21.

TABLE IV. Differences Between Sexes Within the Two Study Groups—Joint Hypermobility at Other Joints, *Habitus* and Orthopedic Traits

Feature	Training center (%)		P-Value
	Females	Males	
Joint hypermobility, other sites			
TMJ	38 (35.8)	8 (44.4)	0.48
2nd–4th MCPs right	68 (64.2)	16 (88.9)	0.04
2nd–4th MCPs left	71 (67.0)	16 (88.9)	0.06
2nd–4th PIPs right	32 (30.2)	8 (44.4)	0.23
2nd–4th PIPs left	42 (39.6)	8 (44.4)	0.70
2nd–4th DIPs right	49 (46.2)	9 (50.0)	0.77
2nd–4th DIPs left	52 (49.1)	9 (50.0)	0.94
MTPs right	40 (40.4)	11 (61.1)	0.10
MTPs left	40 (40.4)	12 (66.7)	0.04
Ankle right	29 (29.3)	3 (16.7)	0.39
Ankle left	29 (29.3)	3 (16.7)	0.39
Hip right	43 (43.4)	6 (33.3)	0.42
Hip left	43 (43.4)	6 (33.3)	0.42
Neck rotation right	33 (32.4)	5 (33.3)	0.99
Neck rotation left	30 (29.4)	5 (33.3)	0.76
Neck flexion right	45 (44.1)	12 (80.0)	0.009
Neck flexion left	44 (43.1)	12 (80.0)	0.008
Full spine rotation right	65 (63.7)	13 (86.7)	0.08
Full spine rotation left	65 (63.7)	13 (86.7)	0.08
Full spine flexion right	34 (33.3)	8 (53.3)	0.13
Full spine rotation left	36 (35.3)	8 (53.3)	0.18
Total	15–18	99–102	
Habitus (BMI)			
Leptosomic	14 (15.6)	1 (16.7)	0.99
Picnic	22 (24.4)	1 (16.7)	0.99
Total	90	6	
Habitus (arm span)			
Dolichostenomelia	24 (23.3)	6 (33.3)	0.38
Brachymelia	11 (10.7)	1 (5.6)	0.69
Total	103	18	
Wrist sign			
Right	24 (22.9)	2 (12.5)	0.52
Left	24 (22.9)	3 (18.8)	0.99
Monolateral	4 (3.8)	1 (6.3)	0.51
Bilateral	22 (21.0)	2 (12.5)	0.74
Total	105	16	
Thumb sign			
Right	10 (9.5)	1 (5.9)	0.99
Left	14 (13.3)	0 (0.0)	0.21
Monolateral	4 (3.8)	1 (5.9)	0.53
Bilateral	10 (9.5)	0 (0.0)	0.35
Total	105	17	
Orthopedic traits			
FDSDU right	73 (69.5)	8 (44.4)	0.04
FDSDU left	76 (71.7)	10 (55.6)	0.17
1st MCP subluxation right	6 (5.7)	1 (5.6)	0.99
1st MCP subluxation left	4 (3.8)	1 (5.6)	0.55
<i>Pectus carinatum</i>	3 (2.9)	2 (11.1)	0.11
<i>Pectus excavatum</i>	5 (4.9)	4 (22.2)	0.03
Dorsal hyperkyphosis	70 (66.0)	13 (76.5)	0.39
Lumbar hyperlordosis	75 (70.8)	11 (61.1)	0.41
Scoliosis (<20 degrees)	60 (56.6)	7 (38.9)	0.16
Cubitus valgus right	60 (56.6)	5 (27.8)	0.02
<i>Cubitus valgus</i> left	51 (48.1)	1 (5.6)	0.001

(Continued)

TABLE IV. (Continued)

Feature	Training center (%)		P-Value
	Females	Males	
<i>Genuum valgus</i> right	52 (49.1)	9 (50.0)	0.94
<i>Genuum valgus</i> left	54 (50.9)	10 (55.6)	0.72
Flexible flatfoot right	58 (54.7)	14 (77.8)	0.07
Flexible flatfoot left	54 (50.9)	13 (72.2)	0.09
In-toeing gait right	6 (5.7)	4 (23.5)	0.03
In-toeing gait left	6 (5.7)	4 (23.5)	0.03
<i>Hallux valgus</i> right	32 (30.5)	1 (5.9)	0.04
<i>Hallux valgus</i> left	33 (31.4)	2 (11.8)	0.15
Total	105–106	18	

Significant *P*-values below 0.01 are indicated in bold.

Comparison by sex was not possible in the validation center due to the small number of patients.

DIP, distal interphalangeal (joint); MCP, metacarpophalangeal (joint); MTP, metatarsophalangeal (joint); NA, not available; PIP, proximal interphalangeal (joint); TMJ, temporomandibular joint.

DISCUSSION

The leading purpose of this study is nosologic. Since the publication of the two currently available diagnostic criteria for JHS and EDS-HT in the late '90s [Beighton et al., 1998; Grahame et al., 2000], too little attention has been paid to the features detectable on physical examination. In fact, in the last 5 years the number of publications on JHS/EDS-HT has multiplied, but many of them were limited to analyzing subjective symptoms or variables influencing quality of life. However, thanks to the efforts of a few research groups, JHS/EDS-HT is now a complex and truly “systemic” disorder overlapping functional gastrointestinal disorders [Zarate et al., 2010] and cardiovascular dysautonomia [De Wandele et al., 2014]. Pain generation and modulation in JHS/EDS-HT is a further promising field of research in this condition [Rombaut et al., 2015b]. It is likely that JHS/EDS-HT probably will remain for years a clinical diagnosis recognized during consultation by accurate physical examination. Now, it is clear enough that there is a lack of consensus concerning the application of Brighton and Villefranche criteria and BS also among experts and such a confusion is influenced by the lack of clinical research on the physical phenotype and natural history of JHS/EDS-HT [Remvig et al., 2014; Castori et al., 2014b]. The phenotypic continuity from apparently isolated GJH on one end and JHS/EDS-HT on the other is difficultly managed also in specialized setting, and this lays on the gap between available diagnostic criteria and the increasing knowledge accumulated in the last years.

The inverse relationship between age at diagnosis and ROM and, consequently, BS is known since 2007 [Remvig et al., 2007]. In the present study, we confirmed that in Italian JHS/EDS-HT patients, the BS is lower in adults and is often in the “negative” range (i.e., <5) since the fourth decade of life [Castori et al., 2011, 2014a, 2015]. This means that pediatric and young adult patients commonly have a “positive” BS at first ascertainment. Then, in the presence of the typical but variable skin changes, they can be labeled as EDS-HT according to Villefranche criteria. In the meantime, adults and the elder rarely maintain or obtain a formal diagnosis of EDS-HT due to their often low BS. Age was demonstrated as a primary confounding factor in the mutual application of Brighton and Villefranche criteria in a pedigree study on 23 families with

JHS/EDS-HT [Castori et al., 2014a]. In this work, most families showed a non-homogeneous distribution of the two clinical diagnoses among the different generations, with an excess of EDS-HT “alone” in children and JHS in adults and elders, and possibility of co-morbidity in adolescents and middle-aged patients.

The question whether a patient with the suspect of a systemic disorder has (had) or not GJH is relevant. In fact, the differential diagnosis of such “complex” patients is not straightforward and often include many rheumatologic and non-rheumatologic disorders. In the presence of GJH and in the absence of chronic inflammation, the diagnosis of JHS/EDS-HT is likely. The negative effect of age on ROM was known in the past [Grahame et al., 2000; Remvig et al., 2007]. Probably in line with such an assumption, the Brighton criteria, which were originally defined in an adult rheumatologic setting, include a lower BS (≥ 4) compared to the Villefranche criteria (≥ 5) as a major criterion and also consider a BS value of 1–3 as a minor criterion. In addition, a simple 5-point questionnaire was subsequently “unofficially” introduced in order to historically check for GJH in symptomatic or asymptomatic patients who have lost their earlier hypermobility [Hakim and Grahame, 2003].

In this study, we observed that age at diagnosis has some relationship with the single items of the BS, as well as with the ROM of 21 additional joints or group of joints. While the BS tends to be lower in adults and elder in both groups, the link between age at ascertainment and the presence/absence of the single BS items is different in the two patients' cohorts. In particular, the presence of seven out of the nine maneuvers of the BS associate with a lower mean age at diagnosis in the TC only. Furthermore, the mean BS is overall higher in the TC than VC. The reasons for such a difference remain obscure. Interestingly, while in the TC the BS was assessed by the use of an orthopedic goniometer, this was not the case of the VC where the evaluation of ROM was clinical. It may be inferred that the routine use of an orthopedic goniometer may contribute to this heterogeneity. Anyway, further elements, such as small sample size, different personnel/centers, lack of standardization and not comparable training background, could have influenced the divergent results on BS between the two centers. In addition, there are more differences between the TC and VC and no attempt was carried out to explore the inter-examiner variability. This study confirms the lack of a consensus in the assessment of the BS also

TABLE V. Age Effect on Dislocations and Soft-Tissue Injuries

Feature	Training center (%)				Validation center (%)				P-Value
	≤20 years	21–30 years	31–40 years	>40 years	≤20 years	21–30 years	31–40 years	>40 years	
Dislocations									
1–2	6 (16.7)	3 (15.0)	2 (6.3)	2 (5.6)	1 (7.1)	0 (0.0)	1 (8.3)	5 (20.0)	0.24
3–10	2 (5.6)	2 (10.0)	8 (25.0)	9 (25.0)	2 (14.3)	2 (14.3)	1 (8.3)	8 (32.0)	0.28
>10	12 (33.3)	7 (35.0)	11 (34.4)	12 (33.3)	5 (35.7)	7 (50.0)	3 (25.0)	3 (12.0)	0.07
Habitual/recurrent	1 (2.8)	4 (20.0)	2 (6.3)	1 (2.8)	1 (7.1)	4 (28.0)	2 (16.7)	3 (12.0)	0.42
More than 2	15 (41.7)	13 (65.0)	21 (65.6)	22 (61.1)	8 (57.1)	13 (92.8)	6 (50.0)	14 (65.0)	0.07
Fingers	1 (2.8)	4 (20.0)	3 (9.4)	1 (2.8)	3 (21.4)	0 (0.0)	1 (8.3)	0 (0.0)	0.04
Wrists	4 (11.1)	1 (6.0)	1 (3.1)	3 (8.3)	2 (14.3)	3 (21.4)	0 (0.0)	2 (8.0)	0.32
Elbows	5 (13.9)	0 (0.0)	2 (6.3)	2 (5.8)	1 (7.1)	1 (7.1)	0 (0.0)	3 (12.0)	0.64
Shoulders	11 (30.6)	6 (30.0)	10 (31.3)	11 (30.6)	5 (35.7)	12 (85.7)	7 (58.3)	9 (36.0)	0.01
Heels	1 (2.8)	2 (10.0)	4 (12.5)	4 (11.1)	2 (14.3)	1 (7.1)	2 (16.7)	4 (16.0)	0.87
Knees/rotulae	5 (13.0)	5 (25.0)	9 (28.1)	3 (8.3)	3 (21.4)	3 (21.4)	2 (16.7)	5 (20.0)	0.99
Hips	7 (19.4)	7 (35.0)	7 (21.9)	10 (27.8)	3 (21.4)	7 (50.0)	3 (25.0)	6 (24.0)	0.29
TMJ	5 (13.9)	6 (30.0)	11 (34.4)	10 (27.8)	3 (21.4)	6 (42.9)	7 (58.3)	12 (48.0)	0.26
Vertebrae	0 (0.0)	1 (5.0)	1 (3.1)	1 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.0)	0.35
Ribs	0 (0.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.0)	0.65
Total	36	20	32	36	14	14	12	25	
Major sprains									
1–2	4 (11.1)	0 (0.0)	4 (12.5)	2 (5.6)	1 (7.1)	0 (0.0)	5 (41.7)	4 (16.0)	0.02
3–10	6 (16.7)	2 (10.0)	6 (18.8)	4 (11.1)	5 (35.7)	3 (21.4)	1 (8.3)	4 (16.0)	0.33
>10	7 (19.4)	9 (45.9)	13 (40.6)	18 (50.0)	5 (35.7)	5 (35.7)	2 (16.7)	9 (36.0)	0.65
Habitual/recurrent	1 (2.8)	1 (5.0)	0 (0.0)	3 (8.3)	1 (7.1)	0 (0.0)	3 (35.0)	2 (8.0)	0.16
>2	14 (38.9)	12 (60.0)	19 (59.4)	25 (69.4)	11 (78.6)	8 (57.1)	6 (50.0)	15 (60.0)	0.47
Fingers/wrists	4 (11.1)	1 (5.0)	3 (9.4)	4 (11.1)	1 (7.1)	2 (14.3)	1 (8.3)	2 (8.0)	0.91
Elbows	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.8)	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0.30
Heels	17 (47.2)	12 (60.0)	19 (59.4)	27 (75.0)	10 (71.4)	8 (57.1)	5 (41.7)	15 (60.0)	0.49
Knees	3 (8.3)	3 (15.0)	5 (15.6)	4 (11.1)	2 (14.3)	3 (21.4)	5 (41.7)	7 (28.0)	0.44
Total	36	20	32	36	14	14	12	25	
3 or more soft tissue injuries									
Feature	3 (8.3)	8 (40.0)	14 (42.8)	21 (58.3)	4 (28.6)	5 (35.7)	5 (41.7)	12 (48.0)	0.67
Total	36	20	32	36	14	14	12	25	

Significant P-values below 0.01 are indicated in bold.
TMJ, temporomandibular joint.

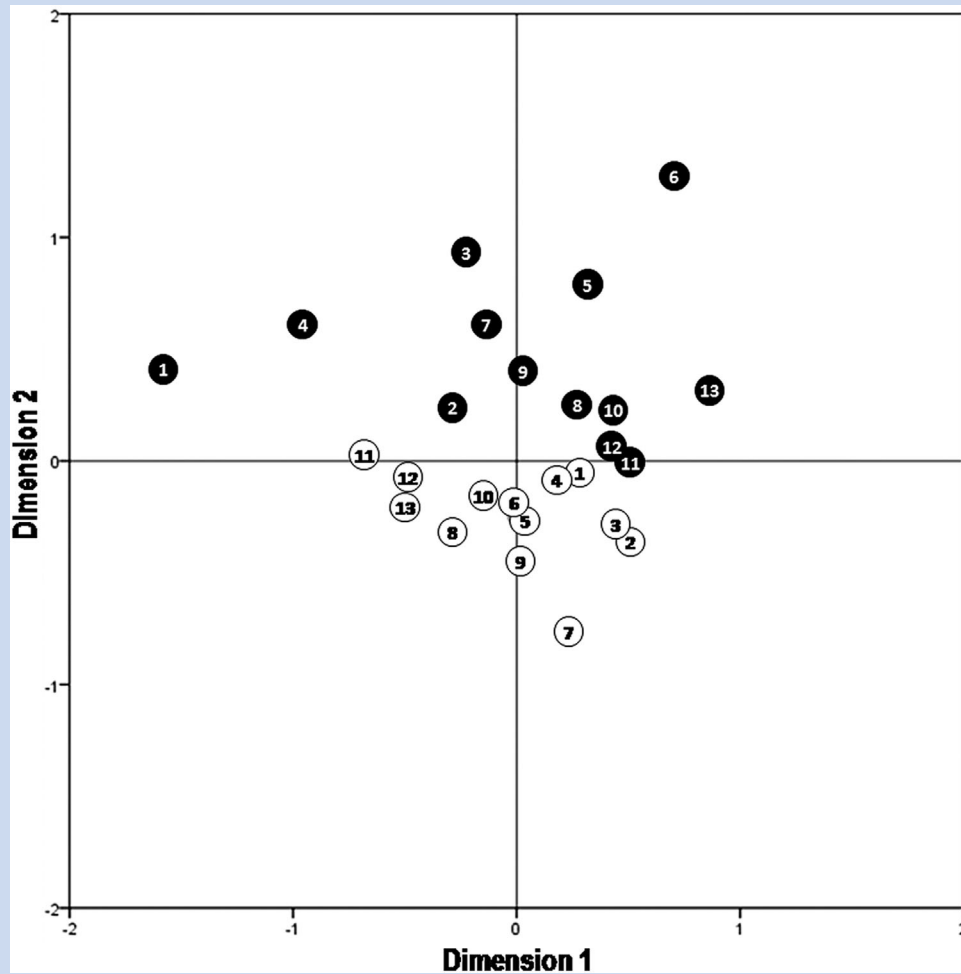


FIG. 4. Multiple correspondence analysis for sex, Beighton score (as a dichotomic trait; i.e., ≥ 5 vs. < 5) and eleven traits at physical examination. All features are indicated by a circle with black circles indicating presence and white circles indicating absence. This analysis was carried out in the training center only. Symbol legend: 1 = sex (black = males; white = females); 2 = Beighton score (black = ≥ 5 ; white = < 5); 3 = arm span (black > 1.03 ; white = < 0.97); 4 = sternum deformities (black = yes; white = no); 5 = thumb sign (black = yes; white = no); 6 = wrist sign (black = yes; white = no); 7 = flexible flatfoot (black = yes; white = no); 8 = cubitus valgus (black = yes; white = no); 9 = genuum valgus (black = yes; white = no); 10 = hallux valgus (black = yes; white = no); 11 = recurrent dislocations (black = yes; white = no); 12 = recurrent sprains (black = yes; white = no); 13 = recurrent soft-tissue injuries (black = yes; white = no). Dimension 1 and dimension 2 indicate the Euclidean spatial nature of the multiple correspondence analysis.

among “expert” centers [Remvig et al., 2014] and the need of more extended and multicentric studies for solving the issue.

A link between age at ascertainment and ROM of the 21 extra joints outside the BS is also evident. The mean age of patients showing hypermobility in many of these joints is significantly lower than the mean age of those with normal mobility at the same sites. This occurs in all joints but not in ankles, MTP joints, TMJ, and spine (in rotation), whose mobility, in turn, seemed less affected by age. However, such a phenomenon is lost at multivariate logistic regression analysis except for spine rotation on the left. Therefore, the search for joints less influenced by age in order to identify a more reliable scoring system for assessing GJH at different ages

results prohibitive. In order to more accurately assess for the presence or absence of GJH, the routine evaluation of joints outside the BS may be helpful, especially when a full BS cannot be obtained due to non-collaborative or disabled patients, or in presence of a negative BS but a positive 5-point questionnaire.

Concerning joint instability complications, there is not any overt association between age at ascertainment and their rate and location. Multivariate logistic regression analysis demonstrated a link between age at diagnosis and presence of three or more soft tissue injuries only. Therefore, recurrent joint dislocations remain a valid marker for JHS/EDS-HT although a consensus is still lacking concerning number of dislocations and of affected joints for the

TABLE VI. Positive Results of the Multivariate Logistic Regression Analysis

Feature	Sex		Age		Center	
	OR (CI 95%)	P	OR (CI 95%)	P	OR (CI 95%)	P
Habitus, picnic	1.05 (0.20–5.60)	0.95	1.06 (1.02–1.09)	0.001	1.10 (0.49–2.49)	0.81
Beighton score						
1st finger right	0.97 (0.30–3.10)	0.95	0.94 (0.91–0.96)	< 0.0001	3.08 (1.54–6.16)	0.001
1st finger left	0.78 (0.25–2.49)	0.68	0.94 (0.92–0.97)	< 0.0001	3.44 (1.73–6.85)	< 0.0001
5th finger right	1.74 (0.51–5.99)	0.38	0.94 (0.92–0.97)	< 0.0001	9.36 (4.27–20.51)	< 0.0001
5th finger left	0.96 (0.30–3.09)	0.94	0.95 (0.93–0.97)	< 0.0001	5.61 (2.78–11.34)	< 0.0001
Elbow right	1.51 (0.60–3.87)	0.38	0.98 (0.96–0.99)	0.03	0.32 (0.17–0.61)	0.001
Elbow left	0.91 (0.35–2.33)	0.84	0.96 (0.94–0.98)	< 0.0001	0.71 (0.38–1.34)	0.29
Knee right	0.89 (0.33–2.36)	0.81	0.96 (0.94–0.99)	0.001	3.46 (1.77k6.76)	< 0.0001
Knee left	1.18 (0.44–3.14)	0.75	0.97 (0.94–0.99)	0.001	2.74 (1.43–5.23)	0.002
Spine	0.40 (0.15–1.06)	0.07	1.01 (0.98–1.02)	0.98	0.54 (0.29–0.99)	0.05
Hypermobility, other joints						
2nd–4th DIPs right	0.43 (0.13–1.41)	0.16	0.95 (0.92–0.98)	< 0.0001	NA	NA
2nd–4th DIPs left	0.34 (0.10–1.16)	0.08	0.95 (0.92–0.97)	< 0.0001	NA	NA
2nd–4th PIPs right	0.64 (0.19–2.13)	0.47	0.94 (0.91–0.97)	< 0.0001	NA	NA
2nd–4th PIPs left	0.41 (0.12–1.37)	0.15	0.94 (0.92–0.97)	< 0.0001	NA	NA
2nd–4th MCPs right	1.68 (0.31–9.05)	0.55	0.94 (0.92–0.97)	< 0.0001	NA	NA
2nd–4th MCPs left	1.60 (0.30–8.50)	0.58	0.95 (0.92–0.98)	0.001	NA	NA
Full spine rotation left	2.34 (0.47–11.80)	0.3	0.97 (0.94–1.0)	0.05	NA	NA
Full spine flexion right	1.01 (0.29–3.50)	0.99	0.95 (0.92–0.98)	0.002	NA	NA
Full spine flexion left	0.98 (0.29–3.37)	0.98	0.95 (0.93–0.98)	0.003	NA	NA
Neck rotation right	0.46 (0.12–1.69)	0.24	0.95 (0.92–0.98)	0.003	NA	NA
Neck rotation left	0.44 (0.12–1.66)	0.23	0.94 (0.91–0.98)	0.001	NA	NA
Neck flexion right	1.77 (0.38–8.33)	0.47	0.93 (0.90–0.96)	< 0.0001	NA	NA
Neck flexion left	1.50 (0.29–7.67)	0.63	0.91 (0.88–0.95)	< 0.0001	NA	NA
Hip right	0.23 (0.07–0.82)	0.02	0.95 (0.92–0.98)	0.001	NA	NA
Hip left	0.23 (0.07–0.82)	0.02	0.95 (0.92–0.98)	0.001	NA	NA
Orthopedic traits						
FDSDU right	0.81 (0.25–2.62)	0.72	1.05 (1.02–1.08)	0.002	NA	NA
FDSDU left	1.23 (0.38–4.03)	0.73	1.05 (1.02–1.09)	0.001	NA	NA
1st MCP subluxation right	NA		1.21 (1.08–1.36)	0.001	NA	NA
1st MCP subluxation left	NA		1.16 (1.05–1.28)	0.003	NA	NA
<i>Pectus excavatum</i>	5.83 (1.77–19.27)	< 0.0001	0.96 (0.92–1.01)	0.06	0.34 (0.11–1.02)	0.06
Lumbar hyperlordosis	0.45 (0.17–1.17)	0.1	0.98 (0.95–0.99)	0.03	1.03 (0.53–1.99)	0.93
<i>Cubitus valgus</i> right	0.32 (0.12–0.84)	0.02	0.99 (0.98–1.02)	0.66	1.02 (0.55–1.88)	0.96
<i>Cubitus valgus</i> left	0.11 (0.03–0.40)	< 0.0001	0.98 (0.96–1.01)	0.13	0.96 (0.51–1.80)	0.89
<i>Genuum valgus</i> right	0.84 (0.34–2.09)	0.7	0.99 (0.98–1.02)	0.67	1.88 (1.01–3.51)	0.05
<i>Genuum valgus</i> left	1.58 (0.64–3.91)	0.32	1.01 (0.99–1.03)	0.43	1.85 (1.0–3.44)	0.05
In-toeing gait left	2.62 (0.75–9.17)	0.13	0.96 (0.92–1.0)	0.05	0.72 (0.24–2.20)	0.57
<i>Hallux valgus</i> right	0.99 (0.32–3.13)	0.99	1.05 (1.02–1.07)	< 0.0001	0.58 (0.30–1.14)	0.11
<i>Hallux valgus</i> left	1.25 (0.41–3.76)	1.05	1.05 (1.02–1.07)	< 0.0001	0.55 (0.28–1.08)	0.08
Dislocations						
Number: 3–10	0.59 (0.12–2.84)	0.51	1.04 (1.01–1.06)	0.01	0.88 (0.40–1.93)	0.74
Number: habitual/recurrent	1.21 (0.29–5.05)	0.8	0.99 (0.96–1.03)	0.67	0.37 (0.14–0.99)	0.05
Site: Shoulders	0.67 (0.26–1.77)	0.42	0.99 (0.98–1.02)	0.68	0.43 (0.23–0.79)	0.007
Site: TMJ	0.67 (0.22–2.03)	0.67	1.02 (1.01–1.05)	0.04	0.48 (0.25–0.91)	0.02
Sprains						
Number: >10	0.23 (0.06–0.84)	0.03	1.01 (0.99–1.03)	0.31	1.36 (0.71–2.60)	0.36
Site: knees	2.62 (0.83–8.26)	0.1	1.03 (0.99–1.06)	0.06	0.40 (0.18–0.88)	0.02
Three or more soft tissue injuries	0.50 (0.15–1.64)	0.25	1.05 (1.02–1.07)	< 0.0001	0.98 (0.51–1.89)	0.95

Significant *P*-values below 0.01 are indicated in bold.

CI, confidence interval; DIP, distal interphalangeal joint; FDSDU, fixed dorsal subluxation of the distal ulna; MCP, metacarpophalangeal [joint]; MTP, metatarsophalangeal [joint]; NA, not available; OR, odds ratio; PIP, proximal interphalangeal [joint]; TMJ, temporomandibular joints.

formal attribution of this feature. Sprains are common complications of GJH in Italian patients but the high rate in the general population limits their use as a diagnostic criterion. Based on our preliminary study, recurrent (i.e., ≥ 3) soft-tissue injuries seems a valid marker in adults but might lack sensitivity in children.

According to the generally accepted sex ratio in JHS/EDS-HT [Castori et al., 2010b], females were 6–7 times more highly represented than males also in both study groups. Variable explanations to this phenomenon have been recently put forward, including an autosomal trait with sex-restricted modifying factors, a complex disorder influenced by sexual dimorphism, and genetic heterogeneity also including a X-linked dominant form [Castori et al., 2011, 2014a]. Apparently in contrast with what was previously thought about the predominance of affected females and its simplistic explanation relating to the different muscular build between sexes, in this study JHS/EDS-HT males presented GJH with a similar pattern compared to females (Table IV). This phenomenon remains without a clear explanation, but may be still in line with the tendency of an attenuated phenotype in males. Accordingly, in males symptoms may present less frequently and usually in those with more marked physical manifestations, such as a positive or higher BS. Besides perhaps a slightly significant increase of the mean BS in males, no other physical attribute seems appropriate for distinguishing between sexes.

Typical *habitus* was heterogeneously reported feature of our samples. The role of Marfanoid *habitus* was early recognized and included in the Brighton criteria [Grahame et al., 2000]. More recently, emphasis has been put on arachnodactyly as a powerful marker for heritable connective tissue disorders in the routine rheumatologic clinic [Grahame and Hakim, 2013]. *Habitus* is not included in the Villefranche criteria for EDS-HT and the original *habitus* item from the Brighton criteria does not offer any guidance on the relative weight that dolichostenomelia and arachnodactyly carry in the attribution of the criterion. In our samples, dolichostenomelia, positive wrist sign and positive thumb sign were reported in 25%, 20–24%, and 10–12% of the patients. Interestingly, dolichostenomelia and arachnodactyly did not combine together in our sample (Fig. 4). Therefore, our finding seems suggesting independence of the two sub-features during the assessment of the *habitus* in JHS/EDS-HT. Anthropometry was also independent from the distribution of the subcutaneous fat and BMI. We feel that in the past confusion could had occurred in the distinction between a true Marfanoid *habitus* and a leptosomic built (i.e., BMI < 19). Therefore, accurate anthropometric information is necessary before the attribution of the *habitus* criterion and further consensus is needed concerning the minimal number of positive maneuvers requested for establishing the presence of arachnodactyly. The middle finger length/total hand length ratio could be a useful and more objective surrogate of the wrist and thumb signs but systematic studies are still lacking in JHS/EDS-HT.

In summary, this work highlights the need of applying some adjustments for age concerning the assessment of GJH with minor emphasis on sexual dimorphism; the existence of a very few joints within and outside the BS that show a comparable ROM at the different ages at ascertainment; the high diagnostic value of recurrent and multiple-site dislocations compared with other joint instability complications; and the heterogeneity of orthopedic

manifestations with dolichostenomelia and arachnodactyly occurring independently. We hope that our findings could support the future revision of the criteria presently defining the overlapping phenotypes of JHS and EDS-HT.

ACKNOWLEDGMENTS

The authors thank Prof. Rodney Grahame, Division of Medicine at the University College of London, for having critically revised the manuscript. This project was actively supported by C.E.D.I. Onlus, the Italian Ehlers-Danlos syndrome patients' association.

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