

Symptom and joint mobility progression in the joint hypermobility syndrome (Ehlers-Danlos syndrome, hypermobility type)

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Abstract

Objective

To evaluate progression of symptoms and joint mobility in the joint hypermobility syndrome (JHS) in order to identify specific disease pictures by age at presentation.

Methods

Fifty JHS patients (44 females, 6 males) were evaluated by Beighton score (BS) calculation, and presence/absence and age at onset of 20 key symptoms. Incidence and prevalence rates by age at onset and sex were calculated and compared by chi-square, Fisher's exact test and Mann-Whitney U-test. Relationship between BS and age at examination was evaluated by the Spearman rho correlation. The existence of an age cut-off separating patients with or without a positive BS was analysed by the receiver operating characteristic analysis. Influence of age on the single components of the BS was also investigated.

Results

Except for isolated features, the overall clinical presentation was the same between sexes. In the whole sample, statistically significant differences by age at presentation were registered for fatigue, myalgias, muscle cramps, strains/sprains, dislocations, tendon ruptures, tendonitis, gastroesophageal reflux, chronic gastritis, constipation/diarrhoea and abdominal hernias. A clear inverse correlation between age at examination and BS was demonstrated with an age cut-off fixed at 33 years. Among the components of the BS, spine and elbow joints were not significantly influenced by age.

Conclusions

This study confirmed the existence of a protean clinical history of JHS which may be exemplified in different phases with distinguishable presentations. The knowledge of the peculiarities of each of them will help the practitioner in recognising and, hopefully, treating this condition.

Key words

Ehlers-Danlos syndrome hypermobility type, evolution, joint hypermobility syndrome, natural history

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Introduction

Joint hypermobility syndrome (JHS), previously termed benign joint hypermobility syndrome, is a probably common, though largely unrecognised heritable rheumatologic condition, mainly characterised by joint hypermobility (JHM) commonly assessed by the Beighton score (BS), joint instability complications, widespread chronic pain, and features of chronic fatigue syndrome (CFS), dysautonomia and functional gastrointestinal disorder (1-6). Now, it is known that JHS is undistinguishable from the Ehlers-Danlos syndrome hypermobility type (EDS-HT) (7). The reason(s) as to why, in the past, different terms were used to name the same condition very probably reflect(s) the extreme clinical variability and protean manifestations of symptomatic JHM. The appellation JHS is usually preferred in the rheumatologic clinic and related diagnostic criteria (Brighton criteria) (8) are best applied in nearly-adult, adult patients. Conversely, the Villefranche criteria for EDS-HT were drawn by an international group of paediatricians and clinical geneticists and best fit the presentation of the disorder in the pediatric age (9). The existence of two distinct sets of diagnostic criteria and the common belief that a negative BS allows the exclusion of the diagnosis (10) make JHS/EDS-HT an elusive diagnosis and mirror the limited knowledge about its overall natural history, which is essentially based on expert opinion (2) and small case series (such an example, see ref. no. 11).

The aim of this study was to contribute in tracing the natural history of JHS/EDS-HT in 50 patients with various ages by evaluating the (i) differential incidence of a set of 20 key symptoms, (ii) BS as a whole and fragmented in its single components, and (iii) discrepancies of disease expression between sexes. Obtained results supported previous anecdotal assumptions on some components of the JHS/EDS-HT natural history and offered consistent data to identify more specific management strategies.

Patients and methods

Patients

Patients were enrolled from those at-

tending the multidisciplinary clinic dedicated to the diagnosis and management of joint hypermobility at the Umberto I and San-Camillo-Forlanini Hospitals in Rome (Italy). Those available for the study were evaluated by physical examination and direct questionnaire administration focused on gathering information about the onset of a set of 20 key symptoms encompassing joint, pain, dysautonomic/neurologic, and gastrointestinal features. The selection of these symptoms was essentially based on the experience of three co-authors (MC, CC and FC). Only patients with a confirmed diagnosis of JHS and/or EDS-HT were selected. Diagnosis was based on published diagnostic criteria including the Brighton criteria for JHS (8) and the Villefranche criteria for EDS-HT (9). Patients were included if met at least either one of these two sets. In our clinical practice, the Brighton criteria are the most stringent for young-adult, adult and elder patients, while the Villefranche criteria are the best for individual in the paediatric age. For this study, JHM was mainly assessed applying the BS (1) and no further joint or group of joints other than those comprised in this score was registered. Beighton score 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. Skin/superficial connective tissue features were assessed qualitatively on the basis of accumulated experience. Other heritable connective tissue disorders were excluded clinically. Individuals with a doubtful or incomplete diagnosis were excluded. This implied that a group of patients with features of JHS still insufficient for a firm clinical diagnosis based on available diagnostic criteria, but likely destined to develop full-blown JHS were not included.

Competing interests: none declared.

Statistical analysis

A series of descriptive statistics were used to summarise pertinent study information. Chi-square and Fisher's exact test was performed for the comparison of categorical variables. Comparison between groups of continuous variables was performed using the Mann-Whitney U-test. The analysis of time to event at symptoms was performed according the Kaplan-Meier method in order to calculate the median age at onset of investigated symptoms. The Spearman rho correlation was used to investigate possible relationship between age at examination and BS. By further investigating the relationship between age at examination and joint mobility, the receiver operating characteristic (ROC) analysis was performed in order to find possible optimal age cut-offs capable of splitting patients into groups with residual JHM (*i.e.* BS ≥ 4 or 5) or without (*i.e.* BS < 4 or 5). The level of statistical significance was set at $p=0.05$. The SPSS®(18.0) and MedCalc® (10.0.1) statistical programs were used for all analyses.

Results

Prevalence of features by age and sex

From a total of 90 patients with confirmed JHS/EDS-HT, complete details were available for 50 individuals (44 females and 6 males) with a mean age at diagnosis of 31.58 years (range=10-64 years). Subjects not fulfilling diagnostic criteria for JHS/EDS-HT or diagnosed with other inherited connective tissue disorders were excluded from this study. For the 20 key symptoms, all patients were asked to indicate the approximate age at onset. The full range of age at onset was fragmented in decades. Cumulative prevalence of each symptom by age categories was itemised in Table I. Of note, while 18 out of 20 symptoms showed variable age at onset within our patients' cohort, congenital contortionism and motor delay/clumsiness always were noted in the very first months of life. Table II showed differences in prevalence between sexes for each symptom. Statistically significant differences were noted only for unrefreshing sleep, chronic gastritis and recurrent abdominal pain,

Table I. Cumulative prevalence of reported symptoms by age.

| Features | Age [n (%)] | | | | |
|-----------------------------|-------------|-----------|-----------|-----------|---------|
| | 0–10 yrs | 11–20 yrs | 21–30 yrs | 31–40 yrs | >40 yrs |
| Cong. contortionism* | 40 (80) | 40 (80) | 40 (80) | 40 (80) | 40 (80) |
| Clumsiness/motor delay* | 23 (46) | 23 (46) | 23 (46) | 23 (46) | 23 (46) |
| Chronic fatigue | 14 (28) | 30 (60) | 38 (76) | 41 (82) | 45 (90) |
| Mem./conc. problems | 9 (18) | 23 (46) | 30 (60) | 37 (74) | 41 (82) |
| Unrefreshing sleep | 8 (16) | 28 (56) | 36 (72) | 39 (78) | 42 (84) |
| Chronic arthralgias | 15 (30) | 35 (70) | 41 (82) | 46 (92) | 49 (98) |
| Chronic back pain | 11 (22) | 30 (60) | 37 (74) | 42 (84) | 43 (86) |
| Chronic myalgias | 17 (34) | 29 (58) | 36 (72) | 38 (76) | 41 (82) |
| Muscle cramps | 11 (22) | 27 (54) | 32 (64) | 36 (72) | 38 (76) |
| Strains/sprains | 20 (40) | 33 (66) | 37 (74) | 38 (76) | 38 (76) |
| Joint dislocations | 20 (40) | 33 (66) | 37 (74) | 38 (76) | 38 (76) |
| Tendon ruptures | 5 (10) | 9 (18) | 11 (22) | 12 (24) | 14 (28) |
| Tendonitis | 5 (10) | 20 (40) | 22 (44) | 26 (52) | 28 (56) |
| GER | 10 (20) | 24 (48) | 30 (60) | 35 (70) | 37 (74) |
| Chronic gastritis | 4 (8) | 14 (28) | 20 (40) | 22 (44) | 24 (48) |
| Recurrent abd. pain | 13 (26) | 20 (40) | 27 (54) | 32 (64) | 34 (68) |
| Constipation/diarrhoea | 27 (54) | 30 (60) | 35 (70) | 35 (70) | 36 (72) |
| Abd. hernias | 5 (10) | 7 (14) | 9 (18) | 9 (18) | 10 (20) |
| Paresthesias at extremities | 5 (10) | 24 (48) | 33 (66) | 36 (72) | 39 (78) |
| Recurrent tachycardias | 3 (6) | 22 (44) | 29 (58) | 35 (70) | 39 (78) |

abd: abdominal; cong.: congenital; GER: gastro-esophageal reflux; mem./conc.: memory/concentration; n: number; yrs: years. *: historical features.

Table II. Comparison of symptom prevalence between sexes.

| Feature | Males (n=6) | Females (n=44) | <i>p</i> -value |
|-----------------------------|-------------|----------------|-----------------|
| Cong. contortionism | 4 (66.7%) | 36 (81.8%) | 0.99 |
| Clumsiness/motor delay | 5 (81.8%) | 18 (40.9%) | 0.02 |
| Chronic fatigue | 5 (81.8%) | 40 (90.9%) | 0.56 |
| Mem./conc. problems | 6 (100%) | 35 (79.5%) | 0.93 |
| Unrefreshing sleep | 6 (100%) | 36 (81.8%) | 0.25 |
| Chronic arthralgias | 6 (100%) | 43 (97.7%) | 0.99 |
| Chronic back pain | 4 (66.7%) | 39 (88.6%) | 0.19 |
| Chronic myalgias | 4 (66.7%) | 37 (84%) | 0.29 |
| Muscle cramps | 4 (66.7%) | 34 (77.2%) | 0.60 |
| Strains/sprains | 3 (50%) | 35 (79.5%) | 0.14 |
| Joint dislocations | 5 (81.8%) | 33 (75%) | 0.99 |
| Tendon ruptures | 3 (50%) | 11 (25%) | 0.33 |
| Tendonitis | 3 (50%) | 25 (56.8%) | 0.99 |
| GER | 3 (50%) | 34 (77.2%) | 0.33 |
| Chronic gastritis | 0 (0%) | 24 (54.5%) | 0.02 |
| Recurrent abd. pain | 0 (0%) | 34 (77.2%) | 0.01 |
| Constipation/diarrhoea | 3 (50%) | 33 (75%) | 0.33 |
| Abd. hernias | 0 (0%) | 10 (22.7%) | 0.58 |
| Paresthesias at extremities | 3 (50%) | 36 (72%) | 0.11 |
| Recurrent tachycardias | 3 (50%) | 36 (72%) | 0.11 |

abd: abdominal; cong.: congenital; GER: gastro-esophageal reflux; mem./conc.: memory/concentration; n: number. Significant *p*-values are in bold.

the first being more common in men and the second two in females.

Incidence of features by age and sex

Incidences by age category for each symptom are summarised in Fig. 1. Here, symptoms were grouped into joint, pain, dysautonomic/neurologic and gastrointestinal features. For comparing the differential incidence of se-

lected features by age at onset arbitrary age categories (*i.e.* 0–10 years, 11–20 years and >20 years) were used. Except for congenital contortionism and clumsiness, differences in age at onset were statistically significant for fatigue ($p=0.04$), myalgias ($p=0.03$), muscle cramps ($p=0.02$), strains/sprains ($p<0.0001$), dislocations ($p<0.0001$), tendon ruptures ($p=0.006$), tendoni-

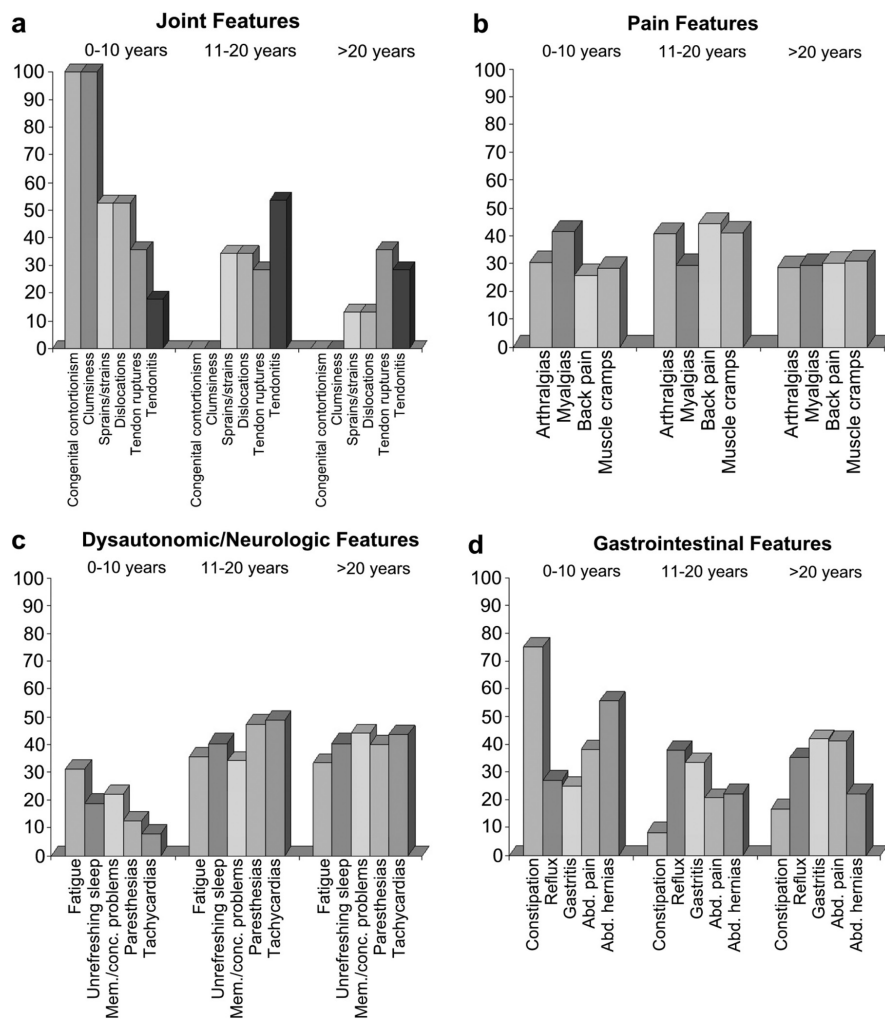


Fig. 1. Onset of reported symptoms by age. Incidence was classified in three groups based on age at onset (*i.e.* 1st decade, 2nd decade and >20 years). Symptoms were organised in four panels including (a) joint features, (b) pain features, (c) dysautonomic/neurologic features, and (d) gastrointestinal features. Values on the vertical lines indicate a percentage.

tis ($p=0.04$), gastroesophageal reflux ($p=0.04$), chronic gastritis ($p=0.04$), constipation/diarrhoea ($p=0.001$), and abdominal hernias ($p<0.0001$).

A positive, though not significant trend was observed for unrefreshing sleep ($p=0.06$). Table III shows median age at onset for each symptom with the respective decade of affiliation. The same table also illustrates differences of median age at onset between sexes. Statistically significant results were noted for unrefreshing sleep only ($p=0.01$).

Joint mobility by age and sex

Figure 2 illustrates the relationship between age at evaluation and BS for the 50 patients. A statistically significant inverse relationship was noted (*i.e.* the BS decreased with the increas-

ing age) with $r(\text{Spearman}) = -0.5$ and $p<0.001$. A similar trend was noted in females with $r(\text{Spearman}) = -0.55$ and $p<0.001$. In males the trend was still visible but values were not statistically significant [$r(\text{Spearman}) = -0.28$, $p=0.59$]. ROC analysis identified a cut-off of 33 years for $BS \geq 5$ or <5 with $p=0.0001$, sensitivity 84.6% and specificity 73% (Fig. 3). The same cut-off (*i.e.* 33 years) emerged for $BS \geq 4$ or <4 but with slightly lower but still significant values ($p=0.008$, sensitivity 85.7% and specificity 65.1%). For 48 patients, BS values of single joints/groups of joint were available. Figure 4 compares age at examination and presence/absence of hypermobility for each of the nine components of the BS. Statistically significant values resulted for

both I fingers, right V finger, and both knees. Positive, though not significant trend was observed for left V finger ($p=0.08$). Comparison between sexes and presence/absence of hypermobility for each of the nine components of the BS was also performed but significant values were obtained for spine only ($p=0.03$).

Discussion

Evolution of joint mobility

Generalised JHM is a common finding in the rheumatologic clinic and may be reported in up to 10–30% of males and 20–40% of females in the general population (12). At the moment, the practitioner is not able to distinguish between subjects with a persisting benign JHM from those who will develop a full-blown JHS. However, it has been estimated that approximately 1 in 10 JHM individuals will sooner or later become JHS patients, with a presumed prevalence of 0.75–2% in the general population (13). Further difficulty is offered by the general assumption that JHM regresses with age (14).

In the present patient sample, we formally demonstrated that BS is inversely related to age (Fig. 2). More interestingly, we also used our data for identifying a possible age cut-off, which was fixed at 33 years, after that patients commonly show negative BS. This means that after this age a JHS/EDS-HT patient likely fails to display JHM according to the BS, while manifests a constellation of associated musculoskeletal and non-musculoskeletal features, as well as, very probably, residual JHM in other joints/groups of joints, such as temporomandibular joint, hips and ankles, not evaluated by this score. Moreover, scrutiny of the weight of the increasing age on single components of the BS was performed (Fig. 4). This demonstrated that some components, including I and V fingers and knees, are negatively influenced by age, while others, including spine and elbows, do not. Such a preliminary evidence, if confirmed and expanded by further studies, may represent a starting point for improving the standard methodology of clinical assessment of JHM by applying age-dependent modifiers,

Table III. Median Age at Onset of Reported Symptoms and Comparison by Sex.

| Feature | Median Age at Onset (years) | | | | |
|----------------------------|-----------------------------|-----------------|------------|--------------|-----------------|
| | Total (CI) | Decade | Males (CI) | Females (CI) | <i>p</i> -value |
| Cong. contortionism | Infancy (NE) | 1 st | NE | NE | NE |
| Clumsiness/motor delay | Infancy (NE) | 1 st | NE | NE | NE |
| Chronic fatigue | 18 (14-22) | 2 nd | 8 (2-14) | 18 (15-21) | 0.43 |
| Mem./conc. problems | 22 (18-26) | 3 rd | 10 (0-24) | 22 (18-26) | 0.21 |
| Unrefreshing sleep | 18 (15-21) | 2 nd | 9 (0-19) | 20 (17-23) | 0.01 |
| Chronic arthralgias | 14 (11-17) | 2 nd | 5 (0-16) | 14 (11-17) | 0.26 |
| Chronic back pain | 17 (12-22) | 2 nd | 23 (8-38) | 16 (11-21) | 0.83 |
| Chronic myalgias | 16 (12-20) | 2 nd | 12 (2-22) | 16 (12-20) | 0.92 |
| Muscle cramps | 18 (13-23) | 2 nd | 15 (5-25) | 18 (9-27) | 0.82 |
| Strains/sprains | 12 (10-14) | 2 nd | 14 (11-17) | 12 (9-15) | 0.49 |
| Joint dislocations | 13 (9-17) | 2 nd | 10 (1-19) | 13 (8-18) | 0.29 |
| Tendon ruptures | 64 (NE) | 4 th | 24 (16-32) | 64 (NE) | 0.05 |
| Tendonitis | 31 (17-45) | 4 th | 31 (19-43) | 26 (13-39) | 0.39 |
| GER | 21 (18-24) | 3 rd | 22 (0-63) | 20 (16-24) | 0.77 |
| Chronic gastritis | 37 (25-49) | 4 th | NE | 33 (18-48) | 0.1 |
| Recurrent abd. pain | 25 (19-31) | 3 rd | NE | 24 (19-29) | 0.12 |
| Constipation/diarrhea | 6 (0-17) | 1 st | 3 (NE) | 6 (0-17) | 0.51 |
| Abd. hernias | NE | 1 st | NE | NE | 0.33 |
| Parestesias at extremities | 20 (16-24) | 3 rd | 30 (NE) | 20 (16-24) | 0.84 |
| Recurrent tachycardias | 24 (18-30) | 3 rd | 35 (NE) | 24 (18-30) | 0.76 |

abd: abdominal; CI: confidence interval; cong.: congenital; GER: gastro-esophageal reflux; mem./conc.: memory/concentration; NE: not evaluable. Significant *p*-values are in bold.

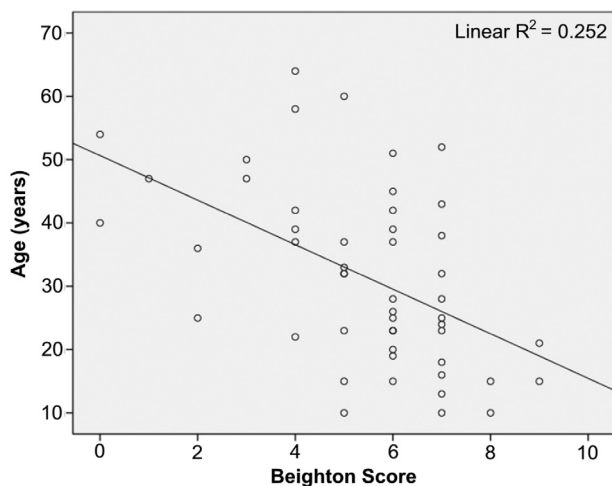


Fig. 2. Scatter plot showing inverse linear correlation between age at examination and Beighton score. Linear R^2 score refers to the whole patients' group.

as partially included in the revised version of the diagnostic criteria for JHS (8). A further clinically validated tool partly addressing this point is a 5-point questionnaire proposed by Hakim and Grahame (15), and aimed at historically investigating JHM in patients having reduced their joint mobility.

Sex influences in disease expression

In the present patient sample the female:male ratio was 7:1 and this evidence supports the well-consolidated concept that both JHM and JHS are more common in females (16). Considering JHS/EDS-HT a Mendelian

trait being transmitted in an autosomal dominant or, more rarely, recessive inheritance patterns, one could hypothesise that sex skewing is determined by disease underestimation among male relatives of the index case, who is often female. However, in an exploratory study we demonstrated that also after careful scrutiny of the apparently unaffected family members the female:male ratio remained skewed, with females being five times more commonly affected (16). Therefore, on a genetic perspective, the discrepancy in disease rate between sexes appears a matter of penetrance rather than expressiv-

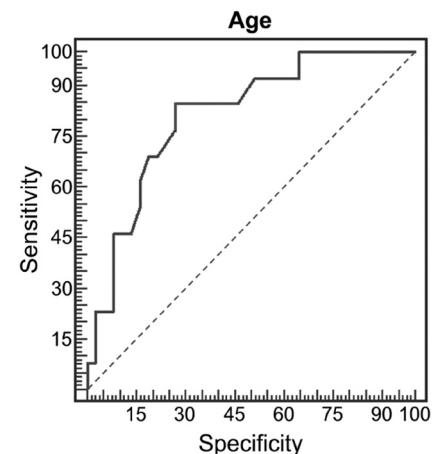


Fig. 3. Receiver operating characteristic (ROC) curve demonstrating the presence of a statistically significant cut-off at 33 years distinguishing patients with a Beighton score ≥ 5 from those with a Beighton score < 5 .

ity. Accordingly, in the present work, comparisons of symptom prevalence and age at onset between sexes (Tables II and III) failed to demonstrate significant divergences, except for clumsiness appearing more common in males, chronic gastritis and recurrent abdominal pain being more typical of females, and unrefreshing sleep having an earlier onset in males. This supports once more that JHS/EDS-HT is probably a Mendelian disease influenced by sex. Concerning joint mobility, the role of sex influence needs a particular mention. In fact, while we noted similar age-related trends of JHM between sexes, the decrease of joint mobility after teenage years is usually more pronounced among males (17). This should be taken into account by the consulting rheumatologist when evaluating male adults with suspected JHS/EDS-HT.

The various phenotypic modulators directly linked to sexual dimorphism are not very likely the unique contributors to sex skewing. Alternatively to the concept of a simple Mendelian inheritance for JHS/EDS-HT, a threshold model could be evoked, in which a single Mendelian inherited mutation represents a major "susceptibility" locus. This mutation is not sufficient *per se* in causing the disease, but other genetic and/or acquired factors, such as sex, sport training, traumas inducing temporary immobility and efficiency of proprioceptive modulation of the mus-

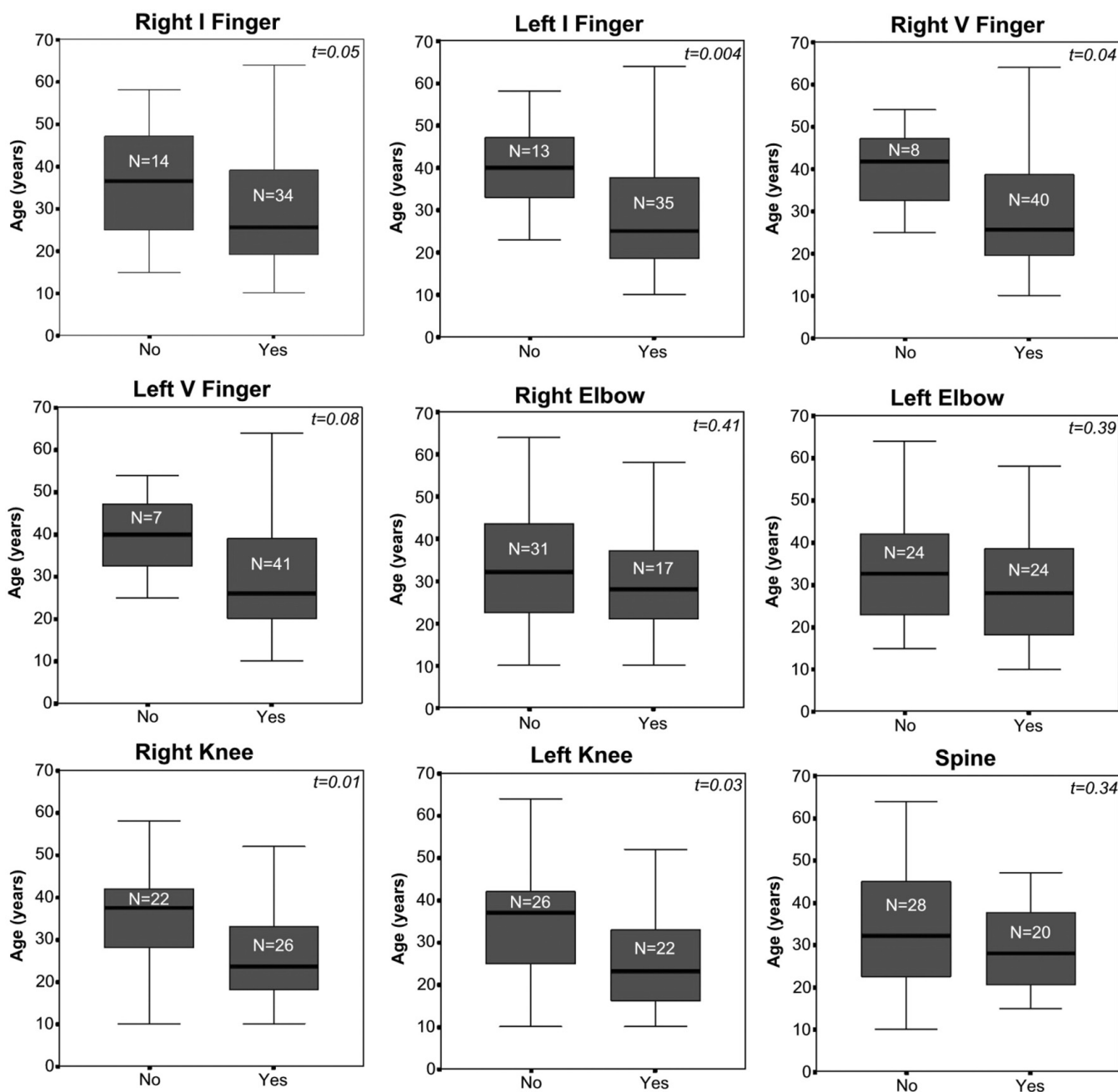


Fig. 4. Box plots comparing the presence (yes) and absence (no) of joint hypermobility at the single components of the Beighton score in relation with age at examination. The horizontal black line indicates the median value, the upper box the first quartile, the lower box the remaining three quartiles, and the vertical line the entire range of values observed in the patient sample.

cle tone, may contribute in reaching the threshold for disease expression. On the other hands, other acquired factors, such as joint injuries and surgery, may work in prematurely decreasing joint range in an hypermobile (and possibly symptomatic) subject. Whatever the genetic contributor to disease manifestations is, our observation also implies that the management and, hopefully, the preventive strategies that in the future could be applied for intercepting

asymptomatic subjects destined to develop more severe symptoms should be similar for both sexes.

Delineation of three disease phases

One of the most relevant problems in recognising and, consequently, managing JHS is its marked clinical variability, observable also in a single patient at different times. Congenital JHM decreases with age, as previously emphasised, and many symptoms are age

dependent with a catastrophic progression during the years (Table I). This peculiar evolution was recently depicted in a dedicated monography (2) and this prompted to delineate at least three discrete phases of the disease, namely “hypermobility”, “pain” and “stiffness”, which may be observed or historically reconstructed in many patients (11). However, this relatively consolidated concept has never been systematically investigated.

In this patients' sample the first decade (0–10 years) of life was dominated by congenital contortionism (80%) and motor delay and/or clumsiness (46%). This combination of features determines the paradoxical association of predisposition to some sports, such as gymnastics and ballet, in a child with delayed motor attainment and lack of balance, and consequent difficulties in some daily activities such as running. This dyad is shared with other inherited disorders, such as congenital myopathies/muscular dystrophies. However, in the latter the progressive course (especially in forms with early onset), developing malaise (chronic fatigue is registered in 28% only of the JHS/EDS-HT patients at this age), muscle hypotrophy/hypertrophy and reduced stamina ease differential diagnosis, which could need further investigations such as plasma creatine phosphokinase dosage, electromyography and muscle biopsy in specific cases, as sometimes occurred in our patients in the paediatric age. Constipation/diarrhoea was a further common finding at this age. However, this feature is unspecific and quite common in the general population (especially among hypotonic subjects like JHS/EDS-HT children), and is of little help for early recognition of JHS/EDS-HT. Although not specifically investigated in this work, easy bruising was observed in 67.4% of patients with shared features of JHS/EDS-HT and chronic fatigue syndrome (6). As this finding is often observed in infancy/childhood, when in association with congenital contortionism and motor delay/clumsiness significantly increases their specificity. The same is valid for abdominal hernias. However, its overall low prevalence in JHS/EDS-HT makes it a too rare finding for being considered a consistent diagnostic clue. Joint dislocations, sprains and strains were reported in 40% of the patients at this age, while other complications are rare. Pain features are uncommon in infancy/childhood, being observed in no more than 1/3 of the sample. Although their frequency in adulthood is high (see below) and this justifies the presence of persisting polyarticular pain among the JHS major criteria for JHS

(8), the same is not true for the EDS-HT criteria (9), in which chronic articular pain is considered a minor item. In the second decade of life the phenotype evolves. Besides JHM, which may be still observed by physical examination, more than half of the patients displays many components of a mixed phenotype gathering features of widespread chronic pain syndrome (arthralgias, myalgias, back pain, muscle cramps), CFS/fibromyalgia (unrefreshing sleep, memory/concentration problems, chronic fatigue) and functional gastrointestinal disorder (gastroesophageal reflux, chronic gastritis, recurrent abdominal pain, constipation/diarrhoea). Taken together, all these features, and particularly chronic fatigue and pain (18), represent major determinants for such a severe deterioration of the quality of life (19). Many of these features, as well as peripheral paresthesias and tachycardia/palpitations both increasing in rate in this decade and exploding in the subsequent years, may be related to dysautonomia, which is now considered a relatively common pathogenic mechanism underlying many apparently unexplained symptoms of JHS/EDS-HT (20). Finally, joint complications increase, especially in form of chronic/recurrent tendonitis. In the subsequent decades, most dysautonomic and pain symptoms highly reported in the second decade become nearly universal. Jointly to this, JHM dramatically decrease with a fixed cut-off of 33 years for losing a positive BS (either 4 or 5 and above). This phase is the most difficult to assess, as the frequent absence of residual generalised JHS needs the use of other and possibly non-musculoskeletal findings for establishing the diagnosis. Although the revised set of Brighton criteria (8) clearly includes some extra-articular findings among the minor criteria, recent advances in the definition of the JHS/EDS-HT clinical spectrum impose further review of the clinical tools actually available for detecting this so protean condition. This work does not address the problem of symptom intermittence over the years. In other words, some features, such as gastritis, may represent a relevant historical

Table IV. Common presentations of JHS/EDS-HT by disease phases.

| Disease phase | Features |
|---------------|---|
| First phase | Congenital contortionism Clumsiness/motor delay Joint dislocations Recurrent sprains/strains Constipation/diarrhoea Abdominal hernias |
| Second phase | Persistent joint pain Chronic/recurrent articular/muscle pain Muscle cramps Chronic fatigue Joint dislocations Recurrent sprains/strains Tendonitis Constipation/diarrhoea |
| Third phase | Progressive loss of joint hypermobility Chronic articular/muscle pain Muscle cramps Chronic fatigue Unrefreshing sleep Tendon ruptures Various gastrointestinal functional features Tachycardias/palpitations Paresthesias at limbs |

feature no longer present at time of evaluation. Therefore, the practicing rheumatologist must take in consideration historical data equally to clinical evidence.

Conclusions

In conclusion, this provisional work supports the general concept of an evolving phenotype for JHS/EDS-HT, in which distinct disease phases may be roughly delineated. The limited sample number hamper some generalisations of presented data, especially in terms of gender influence in disease expression. However, intersection of prevalence and incidence rates for investigated features with data on the evolution of joint mobility permitted to identify a set of discrete findings more commonly encountered in or characteristic of these phases (Table IV). The authors hope that this preliminary work will nurture further clinically-oriented works aimed at investigating the phenotypic variability of JHS/EDS-HT in an attempt to identify novel and more tailored therapeutic strategies for this condition.

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