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ORIGINAL ARTICLE

Unexpected association between joint hypermobility syndrome/Ehlers–Danlos syndrome hypermobility type and obsessive–compulsive personality disorder

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Abstract Joint hypermobility syndrome/Ehlers–Danlos syndrome hypermobility type (JHS/EDS-HT) is a largely unrecognized, heritable connective tissue disorder, mainly characterized by joint instability complications, widespread musculoskeletal pain, and minor skin features. In a case–control study, 47 consecutive JHS/EDS-HT patients were investigated for the prevalence of psychiatric disorders and compared to 45 healthy controls in a single center. The psychiatric evaluation consisted of structured clinical interview for DSM-IV criteria by using the SCID-I and the SCID-II. Symptom severity was assessed using the Hamilton Anxiety Rating Scale (HAM-A), the Hamilton Depression Rating Scale (HAM-D), and the Brief Psychiatric Rating Scale (BPRS). The Global Assessment of Functioning Scale (GAF) was used to assess the overall severity of psychological, social, and occupational functions. JHS/EDS-HT patients had significantly higher mean scores for all questionnaires: HAM-A (6.7 vs. 3.8), HAM-D (6.4 vs. 2.7), GAF (75.0 vs. 86.1), and BPRS (27.5 vs. 25.6). The JHS/EDS-HT group had a 4.3 higher risk of being affected by any psychiatric disorder, and in particular, a 5.8 higher risk of having a personality disorder. In particular, 5 JHS/EDS-HT suffered from obsessive–compulsive personality disorder with an observed prevalence rate of 10.6 % (3.6–23.1). Psychiatric assessment of JHS/EDS-HT patients showed an extremely high prevalence of personality disorders (21 %), and of Axis-I disorders (38 %), mostly depressive. This study did not confirm the previously reported increased rate of panic disorders in JHS/EDS-HT.

Keywords Anxiety disorder · Connective tissue disorder · Depressive disorder · Ehlers–Danlos syndrome · Joint hypermobility · Obsessive–compulsive personality disorder · Personality disorder

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Introduction

Joint hypermobility syndrome (JHS) is a common, but still largely unrecognized, heritable connective tissue disorder, mainly characterized by joint hypermobility (JHM), joint instability, widespread chronic pain, and minor skin features [1]. JHS is now considered one and the same with the Ehlers–Danlos syndrome hypermobility type (EDS-HT) [2] and two clinically undistinguishable disorders. Although still considered a rare condition, the JHS/EDS-HT complex may have a presumed population prevalence ranging from 0.75 to 2 % [3]. JHS/EDS-HT is an exclusion diagnosis based on specific diagnostic criteria [4, 5], but patients' assessment is still hampered by the lack of a confirmatory laboratory test [6]. Historically, the musculoskeletal system is the mostly affected body compartment with an exceptionally high rate of joint complications, such as arthralgias, sprains, strains, subluxations, and dislocations, as well

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as myalgias and fatigue, all symptoms which preluding the development of a chronic widespread musculoskeletal pain syndrome [1, 7]. More recent research points out the existence of a wide variety of extra-articular features, extending but not limited to the cardiovascular, ocular, visceral, and central nervous system [8].

Practice suggests a major role for behavior and psychological health in the development and/or perpetuations of some chronic disabilities in JHS/EDS-HT [9]. In 1994, by studying 48 Ehlers–Danlos syndrome patients (including eleven with EDS-HT and five with JHS), Lumley et al. [10] detected a high rate of anxiety, depression, anger, and interpersonal concerns. Subsequent studies report a considerable excess of emotional symptoms [11] and psychological distress, and somatosensory amplification [12] in JHS/EDS-HT patients. JHS/EDS resulted more common among patients suffering from anxiety and panic disorders, and in turn, these complaints are frequently reported in JHS/EDS-HT [13, 14]. In particular, JHS was diagnosed in 67.7 % of patients with anxiety disorder, while it was demonstrated in 10.1 and 12.5 % of psychiatric patients and controls [15]. In a non-clinical population of 526 subjects, a significant difference for trait anxiety but not for state anxiety was reported [16]. Finally, in a 15-year-follow-up study, Bulbena et al. [17] estimated an absolute risk for panic disorders of 44.1 % among JHS cases compared to 2.8 % for non-JHS subjects. The mechanisms underlying such an association remain obscure. The high rate of medically unexplained symptoms and chronic pain may be a major contributor [8, 9] but it likely does not explain the entire range of behavior/psychiatric features observed in JHS/EDS-HT. Within this gap of knowledge, no data regarding personality disorders and JHS/EDS-HT exist. To further investigate the association between psychiatric disorders and JHS/EDS-HT, we conducted a single-center, case–control study comparing 47 JHS/EDS-HT patients with 45 matched controls with a set of psychiatric tools.

Methods

Forty-seven consecutive patients with JHS/EDS-HT who attended the outpatient clinic at the Physical and Rehabilitation Division, Sapienza University of Rome, between September 2010 and October 2011 were recruited as cases. Controls were 45 healthy subjects of similar age, sex, education, geographical, and social origin recruited from medical students, hospital staff members, and residents in the same period at the Department of Neurology and Psychiatry.

All patients agreed to participate in this study. Diagnosis of JHS/EDS-HT was based on published diagnostic criteria including the Brighton criteria for JHS [5] and the Villefranche criteria for EDS-HT [4] (Table 1). Patients were included if they met at least one of these two criteria sets. In our clinical practice, the Brighton criteria are the most stringent for young-adult, adult, and elder patients, while the Villefranche criteria are best for individuals of paediatric age. For this study, JHS was mainly assessed applying the Beighton score. Beighton score is a nine-point evaluation with the 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 harm), (d) hyperextension of the knee

Table 1 Applied diagnostic criteria in our patients' sample

Brighton criteria (JHS)	Villefranche criteria (EDS-HT)
Major criteria	Major criteria
Beighton score ≥ 4/9	Beighton score ≥ 5/9
Arthralgia for > 3 months in > 4 joints	Skin involvement (hyperextensibility and/or smooth, velvety skin)
Minor criteria	Minor criteria
Beighton score of 1–3	Recurring joint dislocations
Arthralgia in 1–3 joints	Chronic joint/limb pain
History of joint dislocations	Positive family history
Soft tissue lesions > 3	
Marfan-like habitus	
Skin striae, hyperextensibility, or scarring	
Eye signs, lid laxity	
History of varicose veins, hernia, visceral prolapse	
For the diagnosis: both major, or 1 major and 2 minor, or 4 minor criteria and the exclusion of other heritable connective tissue disorders	For the diagnosis: both major features; the presence of one or more minor features was useful for the differential from partially overlapping heritable connective tissue disorders

beyond 10° (one point for each leg), and (e) forward flexion of the trunk with the knee extended and the palm resting flat on the floor. The study was approved by the local ethical committee, and all patients gave their informed consent before participating. Exclusion criteria were severe neurological or clinically significant medical disorders. Clinical and demographic information collected at interview included age, sex, JHS/EDS-HT duration, and medications for other disorders.

The psychiatric evaluation was performed by two trained psychiatrists and was based on the structured clinical interview for DSM-IV criteria using the structured clinical interview (SCID-I) for Axis-I disorders [18] and the SCID-II for Axis-II disorders [19]. The Hamilton Anxiety Rating Scale (HAM-A) [20] was administered to evaluate the severity of anxiety symptoms; the Hamilton Depression Rating Scale (HAM-D) [21] was used to assess the severity of depressive symptoms; the Brief Psychiatric Rating Scale (BPRS) [22] was administered to evaluate the presence of psychotic symptoms. The Global Assessment of Functioning Scale (GAF) [18] was used to assess the overall severity of psychological, social, and occupational functions not related to the presence and severity of EDS-HT. To estimate odds ratios (OR) and 95 % confidence intervals (95 % CI), all these variables were dichotomized as the presence/absence of symptoms or high/low or positive/negative as specified: HAM-A presence $\geq$ 13; HAM-D presence $\geq$ 8; GAF presence $\leq$ 70; BPRS high $\geq$ 25 that corresponds to the upper tercile of controls; SCID-I and SCID-II positive: the presence of at least one symptom. Data are presented as proportions, mean $\pm$ SD, and medians. Two-sample comparisons of proportions were performed by Fisher's exact test; for normally distributed variables, by Student's *t* test; and for non-normally distributed variables, by the Mann–Whitney *U* test. Skewness and kurtosis test were used to assess normality. Considering the low category as the referent, ORs and 95 % CI for the higher category were estimated to asses the likelihood to present the joint hypermobility syndrome. Haldane correction was used where appropriate. Statistical significance was set at $P < 0.05$. The computer package Stata 11 (Stata Corp. LP, College Station, TX, USA) [23] was employed for the statistical analyses.

Results

The mean age of the 92 subjects was 31 years (SD = 13) and 81.5 % were women. The two samples did not differ by sex, age, and years of education (Table 2). JHS/EDS-HT patients collected significantly higher mean scores for all questionnaires HAM-A (6.7 vs. 3.8), HAM-D (6.4 vs. 2.7), GAF (75.0 vs. 86.1), and BPRS (27.5 vs. 25.6) (Mann–Whitney *U* test, $P < 0.01$). This association remained substantially confirmed when scores were dichotomized (Table 3). In particular, subjects with the presence of symptoms according to HAM-A and HAM-D scores were at least 3 times more likely to present JHS/EDS-HT than subjects without symptoms (OR 3.13, 95 % CI 0.92–10.7; OR 3.68, 95 % CI 1.36–10.0, respectively), subjects with the presence of symptoms according to the GAF scale were 8 times more likely to present JHS/EDS-HT than subjects without symptoms (OR 7.93; 95 % CI 2.13–29.5), and subjects with high BPRS scale were 5 times more likely to present JHS/EDS-HT than subjects with low BPRS (OR 5.22, 95 % CI 2.15–12.7).

Joint hypermobility syndrome/Ehlers–Danlos syndrome hypermobility type patients were associated with a higher probability of receiving and/or having received psychiatric treatment (OR 7.04, 95 % CI 2.36–21.0). Estimated ORs

Table 2 Demographic and clinical characteristics of cases and controls

Characteristics	Cases ($N = 47$)	Controls ($N = 45$)	*P* value[a]
Sex no. (%)			
Females	41 (87.2)	34 (75.6)	
Males	6 (12.8)	11 (24.4)	0.18[b]
Age (years)			
Mean	32.4	29.8	
SD	12.7	13.1	0.28
Education no. (%)			
	5 (10.6)	10 (22.2)	
	34 (72.4)	25 (55.6)	
	8 (17.0)	10 (22.2)	0.22[b]
HAM-A			
Mean	6.7	3.8	
SD	6.0	5.5	
Median	6	1	0.008
HAM-D			
Mean	6.4	2.7	
SD	6.4	4.3	
Median	6	0	0.005
GAF			
Mean	75.0	86.1	
SD	6.5	7.3	
Median	75	90	0.001
BPRS			
Mean	27.5	25.6	
SD	3.3	2.8	
Median	27	24	<0.001

HAM-A Hamilton Anxiety Rating Scale, *HAM-D* Hamilton Depression Rating Scale, *GAF* Global Assessment of Functioning Scale, *BPRS* Brief Psychiatric Rating Scale

[a] Mann–Whitney *U* test

[b] Fisher's exact test

for psychiatric diagnosis are illustrated in Table 4. Additional evidence of an higher burden of psychiatric disorders among JHS/EDS-HT cases, as compared to normal controls, is provided in Table 5, which shows an association with any Axis-I psychiatric and any Axis-II personality disorder and a significantly higher likelihood of being an JHS/EDS-HT subject (OR 2.96, 95 % CI 1.17–7.52 and OR 5.81, 95 % CI 1.20–28.2, respectively).

The sample size of our study did not allow us to examine the association with specific DSM categories, since the beta error would be substantial. However, in spite of the low statistical power, we found an association between JHS/EDS-HT and adjustment disorder estimated by the imprecise but significant OR 22.6 (95 % CI 1.3–407.9). We also estimated large, although not significant ORs for major depression OR 11.9 (95 % CI 0.62–231.3), and obsessive–compulsive personality disorder (OCPD) OR 12.8 (95 % CI 0.68–238.4). In particular, we registered OCPD in 5 out of 47 JHS/EDS-HT patients with an overall prevalence of 10.6 % compared to an expected rate in the general population of 2.0 % [24] Accordingly, we did not find OCPD in any of the 45 controls. Since females represent more than 80 % of the study base, we reran the models restricting to this subgroup and the results remain almost the same.

Table 3 Dichotomized HAM-A, HAM-D, GAF, and BPRS by case–control status: ORs and 95 % CI

	Cases ($N = 47$)	Control ($N = 45$)	OR (95 % CI)	*P* value
HAM-A				
Absence	36 (76.6)	41 (91.1)	1 Referent	
Presence[a]	11 (23.4)	4 (8.9)	3.13 (0.92–10.7)	0.07
HAM-D				
Absence	28 (59.6)	38 (84.4)	1 Referent	
Presence[b]	19 (40.4)	7 (15.6)	3.68 (1.36–10.0)	0.01
GAF				
Absence	30 (63.8)	42 (93.3)	1 Referent	
Presence[c]	17 (36.2)	3 (6.7)	7.93 (2.13–29.5)	0.002
BPRS				
Low	14 (29.8)	31 (68.9)	1 Referent	
High[d]	33 (70.2)	14 (31.1)	5.22 (2.15–12.7)	<0.001

HAM-A Hamilton Anxiety Rating Scale, *HAM-D* Hamilton Depression Rating Scale, *GAF* Global Assessment of Functioning Scale, *BPRS* Brief Psychiatric Rating Scale

[a] Presence ≥ 13

[b] Presence ≥ 8

[c] Presence ≤ 70

[d] High ≥ 25, upper tercile of controls

Discussion

In this case–control study, we observed a higher prevalence of psychiatric disorders among subjects affected by JHS/EDS-HT (38 % of Axis-I and 21 % of Axis-II Disorders) as compared to controls. The most interesting finding is that JHS/EDS-HT subjects have a 4.3 relative risk of being affected by any psychiatric disorder. In particular, patients with a previous diagnosis of JHS/EDS-HT have a 5.8 relative risk of having a personality disorder. OCDP was observed in 10.6 % of cases, a rate fivefold higher than the general population [24]. Since OCDP appears significantly more common in JHS/EDS-HT patients, we could speculate on their psychopathologic relationship. In particular, in congenitally hypermobile subjects, the need of a "hyper-control" might be justified by musculoskeletal consequences or associated features, such as joint instability and lack of proprioception [25], which early occur in their life. In addition, perfectionism may result from the frequent

Table 4 Associations between EDS-HT and selected Axis-I and Axis-II psychiatric disorders

Characteristics	Cases ($N = 47$)	Controls ($N = 45$)	All OR (95 % CI)[a]	Females OR (95 % CI)[a]
SCID-I no. (%)				
Major depression	4 (100)	0	11.9 (0.62–231.3)	9.73 (0.50–190.3)
Dysthymia	2 (66.7)	1 (33.3)	2.67 (0.23–31.0)	2.17 (0.18–25.5)
Minor depression	3 (60.0)	2 (40.0)	2.00 (0.31–12.8)	3.25 (0.32–33.4)
Adjustment disorder	8 (100)	0	22.6 (1.25–407.9)	14.1 (0.75–262.9)
Bulimia	1 (50.0)	1 (50.0)	1.33 (0.08–22.3)	1.08 (0.06–18.3)
Panic disorder	2 (50.0)	2 (50.0)	1.33 (0.18–10.1)	0.54 (0.05–6.36)
Anxiety disorder NOS	0	3 (100)	0.19 (0.01–3.82)	0.15 (0.01–3.15)
SCID-II no. (%)				
Narcissistic	1 (100)	0	3.48 (0.14–88.0)	3.10 (0.12–78.9)
OCDP	5 (100)	0	12.8 (0.68–238.4)	11.3 (0.60–213.9)
Histrionic	2 (50.0)	2 (50.0)	1.16 (0.16–8.66)	1.03 (0.14–7.79)
Schizoid	2 (100)	0	5.80 (0.27–124.6)	5.16 (0.24–111.8)

[a] Haldane correction of 0.5 was used for zero cell count

Table 5 Associations between EDS-HT and any Axis-I and Axis-II psychiatric disorders

Characteristics	Cases ($N = 47$)	Controls ($N = 45$)	P value[a]	All OR (95 % CI)	Females OR (95 % CI)
SCID-I no. (%)					
Negative	27 (42.9)	36 (57.1)		1 Referent	1 Referent
Positive	20 (69.0)	9 (31.0)	0.03	2.96 (1.17–7.52)	2.30 (0.84–6.30)
SCID-II no. (%)					
Negative	37 (46.2)	43 (56.8)		1 Referent	1 Referent
Positive	10 (83.3)	2 (16.7)	0.03	5.81 (1.20–28.2)	5.16 (1.05–25.5)
SCID combined no. (%)					
Negative	21 (37.5)	35 (62.5)		1 Referent	1 Referent
Positive (I and/or II)	26 (72.2)	10 (27.8)	0.001	4.33 (1.75–10.7)	3.55 (1.33–9.46)

[a] Fisher's exact test

lack of recognition and poor knowledge of the syndrome by professionals. As suggested by Millon, OCDP is related to having overly controlling parents [26]; thus, in patients affected by JHS/EDS-HT, this kind of hyper-control may involve both parents and patients. Nevertheless, further explanations in order to interpret this association would be too speculative.

The higher frequency of adjustment disorder is not surprising given the chronic and disabling nature of JHS/EDS-HT, as well as the 19 % occurrence of depressive disorders (major depression, minor depression, and dysthymia). Remarkably, we did not observe a higher rate of anxiety disorders, although JHS/EDS-HT still showed higher mean score at HAM-A compared to controls. This finding does not support the findings by Bulbena and co-authors who observed a high rate of panic and other anxiety disorders among JHS patients [17]. Even though panic disorder is a complex condition not simplistically related only to somatic anxiety, the role of cardiovascular dysautonomia might be a confounding factor in JHS/EDS-HT, as previously discussed by other authors [27, 28]. In particular, this feature, usually in the form of postural tachycardia syndrome in JHS/EDS-HT, often presents with dizziness and light-headedness, palpitations, visual disturbances, clamminess, loss of consciousness, nausea, headache, pain (chest or upper abdomen), shortness of breath, and nonspecific symptoms, including fatigue, lethargy, and difficulty thinking or concentrating [29]. When cardiovascular dysautonomia can occur with JHS/EDS-HT, a diagnosis of anxiety disorder according to the DSM-IV criteria could be awkward. An elevated psychological burden in these patients is confirmed by the higher HAM-A, HAM-D, and BPRS scores and by a higher probability of receiving and/or having received psychiatric treatment OR 7.04 (2.36–21.0) as compared to controls.

This case–control study design allowed us to identify significant associations between the preexistent diagnosis of JHS/EDS-HT and specific psychiatric comorbidities. We acknowledge, however, that the relatively small sample size of the study and its low statistical indicate two use caution in generalizing the results. In particular, no firm inference is at moment possible regarding the association between JHS/EDS-HT and selected DSM categories, and further studies are needed to replicate or refine our results. Another limitation is that we cannot rule out a Berkson's bias. In other words, it is possible that, at least for some patients, the observed association is biased by the higher probability of hospital admittance for subjects with a co-diagnosis of JHS/EDS-HT and psychiatric disorder as compared to those with "isolated" JHS/EDS-HT. Nevertheless, as in this study, psychiatric disorders were assessed during and not before hospitalization, the chance of a Berkson's bias appears reduced. In spite of the above-mentioned study limitations, we were able to identify associations, some of the rather strong, between JHS/EDS-HT and psychiatric disorders. The observed associations are clinically relevant and have health care implications. Doctors dealing with JHS/EDS-HT should be made fully aware of the burden of psychiatric disorders present among these patients.

In conclusion, this case–control study showed a higher rate of mood and personality disorders in JHS/EDS-HT compared to matched controls. Among them, the association with OCPD may be of major interest and needs further research. However, our findings highlight the utility of a psychiatric assessment for all JHS/EDS-HT patients in order to better support them in coping with their still poorly investigated disabilities.

Conflict of interest None.

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