INTERNATIONAL JOURNAL OF PSYCHIATRY IN MEDICINE (IN PRESS).

ASSOCIATION BETWEEN PSYCHOPATHOLOGICAL FACTORS AND JOINT HYPERMOBILITY SYNDROME IN A GROUP OF UNDERGRADUATES FROM A FRENCH UNIVERSITY

Carolina Baeza-Velasco[1], Marie-Christine Gély-Nargeot[2], Antonio Bulbena-Vilarrasa[1], Caroline Fénétrier[2] and Jaime F. Bravo[3.]

[1]University Autonomous of Barcelona
[2]University Paul Valéry, Montpellier 3
[3]University of Chile.

ABSTRACT

Objective: To explore the frequency of Joint Hypermobility Syndrome (JHS) among university students and assess whether a relationship exists between this collagen condition and certain psychological variables. *Method*: A cross-sectional sample of 365 undergraduates at a French university was assessed with the Brighton´s criteria for JHS, Somatosensory Amplification Scale (SSAS), Liebowitz Social Anxiety Scale (LSAS) and Hospital Anxiety and Depression Scale (HADS). *Results*: 39.5% of the participants met Brighton's criteria for JHS. Scores of somatosensory amplification were higher among participants with JHS (t =-2.98; p= 0.03) independent of gender. Female participants with JHS had higher scores in depression (t=-2.01; p=0.04) and general anxiety (t=-2.35; p=0.01) than women without JHS. The percentage of males with a medium/high level of social anxiety was greater among participants with JHS (78.6% vs. 41.7%; χ^2=6.18; p=0.01). Logistic regression demonstrated that male sex and low level of somatosensory amplification are variables contrary to the presence of JHS. *Conclusion*: JHS is a frequent condition among young people evaluated. JHS is associated with psychological distress and higher levels of somatosensory amplification.

Key words: joint hypermobility, somatosensory amplification, anxiety, depression

INTRODUCTION

Joint Hypermobility Syndrome (JHS)

Joint hypermobility syndrome (JHS) is considered to be part of a spectrum of Hereditable Disorders of Connective Tissue (HDCT), caused by mutations in gene coding for proteins involved in connective-tissue metabolism. HDCT typically include Ehlers-Danlos syndrome, Marfan syndrome and osteogenesis imperfecta [1]. JHS is a forme fruste of these syndromes and presents some of the features seen in them, although to a lesser degree. JHS seems to be a much milder but a more frequent variation [2]. This collagen condition is characterized by increased distensibility of joints (joint hypermobility) as well as musculoskeletal symptoms such as arthralgias, subluxation or dislocation of joints, tendonitis, bursitis, abnormalities of the skin, myopia, etc. The main complaint of JHS patients is pain. Above all it is an overriding chronic pain in joints, muscles and ligaments, which arise from an inherent predisposition to the effects of everyday trauma [3]. JHS is very frequent but usually undiagnosed [4]. In Spain, JHS constitutes 25% of rheumatological consultations [5]. In Chile, a prevalence of 39% was found [4]. In the UK, rheumatologists' estimates of the number of cases seen annually strongly suggest that the true diagnosis in the majority of patients with JHS is overlooked by up to 95% [6]. To date, there are no published data about the prevalence of JHS in France.

Psychopathological factors in JHS:

Several studies have shown that there is a relationship between JHS and anxiety states; from panic attacks to having a worrier temperament, high levels of subclinical anxiety and authentic phobias [7-13]. Gago [14] observed that subjects with joint hypermobility were eight times more likely to suffer social phobia compared to non-hypermobile. Baeza-Velasco and Bulbena [15] reported that subjects with a greater number of symptoms associated with the JHS had higher levels of social anxiety.

In 2001, Gratacòs et al. [16] described a cytogenetic anomaly common to both joint hypermobility and anxiety disorders. A possible shared biological foundation was considered for the first time. However, subsequent studies have not confirmed this finding [17-19].

To a lesser extent, depression has been also associated with JHS. Lumley, Jordan and Rubenstein [20] reported that depression, anger and interpersonal concerns were significantly elevated in patients with hypermobility. In addition, the experience of chronic pain has been widely associated with depression and distress [21]. According to Lumley et al. [20] the psychological difficulties such ostracism and avoidance of relationships and social activities appear to result from chronic pain and disability.

Ercolani et al. [22] observed that patients with JHS presented more somatic symptoms, general hypochondriasis and disease conviction than healthy subjects. In this regard, it may be relevant to consider the construct of somatosensory amplification [23] to be evaluated in relation to JHS, taking in account that amplification is a common feature of hypochondriasis. Somatosensory amplification refers to the tendency to experience a somatic sensation as intense, noxious, and disturbing. Somatic amplification is characterized by three elements [23, 24]: (I) bodily hypervigilance, which involves increased self-scrutiny and the focus of attention on unpleasant bodily sensations, (II) a tendency to select and focus on certain relatively infrequent sensations and / or faint, and (III) a propensity to value somatic and visceral sensations as abnormal, pathological and indicative of disease, rather than as normal or benign [25]. Amplification significantly contributes to the somatization (or preoccupation with physical sensations) that characterizes hypochondriasis and other psychosomatic disorders, especially panic attacks and panic disorder.

Objectives

The aims of the present study were to observe the presence of JHS in the sample subjects and to analyze the relationship between JHS and psychopathological variables such as anxiety, depression and somatosensory amplification.

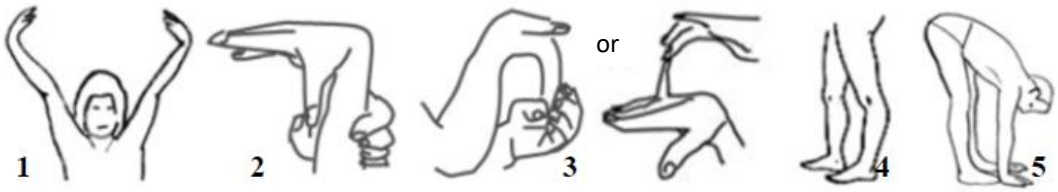
METHOD

Subjects: The subjects were 365 undergraduate students (74 males, 291 females) from the Faculty of Letters at University Paul Valéry 3 of Montpellier. The mean age for the sample was 21.2 years (S.D. = 2.11) and subjects' ages ranged from 18 to 30 years.

Instruments: The Beighton Criteria [26] which consists of five maneuvers with a score range from 0 to 9 (Figure 1). Different experts require a score of between 4 and 6 points out of nine for a positive Beighton score [7], that is, for the patient to be considered as suffering joint hypermobility. For this study we considered a score $\geq$ 5 as indicative of joint hypermobility.

Figure 1. The nine-point Beighton hypermobility score (Beighton et al., 1973).

1. More than 10º hyperextension of the elbows
2. Passively touch the forearm with the thumb, while flexing the wrist.
3. Passive extension of the fingers or a 90º or more extension of the fifth finger (Gorling's sign). This is used as a "Screen Test".
4. Knees hyperextension greater than or equal to 10º (genu-recurvatum)
5. Touching the floor with the palms of the hands when reaching down without bending the knees. This is possible as a result of the hypermobility of the hips, and not of the spine as it is commonly believed.



One point may be gained for each side for maneuvers 1–4 so that the hypermobility score will have a maximum of nine points if all are positive.

The Brighton Criteria [27] for JHS diagnosis. This is a validated set of criteria which consider the nine-point Beighton Score and then take into account symptoms and other indications of connective tissue deficiency (Figure 2). While the structure and content of the criteria remained, some modifications were put in place to adapt the instrument to the collective application; in order to

facilitate self-reporting and the understanding of medical terminology, some brief descriptions were used. For example, tenosynovitis was described as "tendon injury with inflammation"; the word "arthralgia" was replaced by "joint pain", etc. Also each criterion was orally explained by the evaluator.

Figure 2. Brighton criteria for the diagnosis of JHS (Grahame et al. 2000).

MAJOR CRITERIA

1. Beighton score = 4/9* (currently or historically)
2. Arthralgia for longer than 3 months in = 4 joints

MINOR CRITERIA

1. Beighton score = 1, 2, or 3/9 (0, 1, 2, 3 if age > 50 yrs.)
2. Arthralgia in 1–3 joints, or back pain or spondylosis, spondylolysis/spondylolisthesis
3. Dislocation/subluxation in more than one joint, or in one joint on more than one occasion.
4. Soft tissue rheumatism, = 3 lesions (e.g., epicondylitis, tenosynovitis, bursitis)
5. Marfanoid habitus (tall, slim, arm span > height, arachnodactily)
6. Abnormal skin: striae, hyperextensibility, thin skin, papyraceous scarring
7. Eye signs: drooping eyelids or myopia or antimongoloid slant
8. Varicose veins or hernia or uterine/rectal prolapse

JHS is diagnosed in the presence of 2 major criteria, or one major and 2 minor criteria, or 4 minor criteria. Two minor criteria suffice where there is an unequivocally affected firstdegree relative. BJHS is excluded by presence of Marfan or Ehlers-Danlos syndrome (other than the EDS Hypermobility type (formerly EDS III) as defined by the Ghent 1986 and the Villefranche 1998 criteria respectively). Criteria Major 1 and Minor 1 are mutually exclusive, as are Major 2 and Minor 2.

* 5/9 in this study.

The Hospital Anxiety and Depression Scale (HADS) [28] in its French version [29]. This is a 14-item self-report screening scale developed to indicate the possible presence of anxiety and depressive states. It contains two 7-item scales: one for anxiety and one for depression. The anxiety items focus on general anxiety, and five of the items are close to the diagnostic criteria of general anxiety disorder. The depression items are based on anhedonia, which is considered to be one of the essential criteria for depression [6]. It is a standardized and validated instrument [29] which can be used in a variety of settings (e.g. community, primary care, in-hospital, and psychiatry).

The Liebowitz Social Anxiety Scale (LSAS) [30], validated by Yao et al. [31]. The LSAS is a 24-item scale providing separate scores for fear and avoidance in social and performance situations over the past week. This widely used scale is a reliable and valid measure of social phobia [2].

The Somatosensory Amplification Scale (SSAS). Barsky et al. [32] have constructed the SSAS to assess sensitivity to unpleasant but benign somatic sensations. It is a self-applied 10-item questionnaire. The respondents rate the degree to which each statement is "characteristic of you in general", on an ordinal scale of 1 to 5. A higher total score indicates greater symptom amplification. In this study we used the cut-off point of 29 (score range from 10 to 50) proposed by Bridou and Aguerre [33] in its French adaptation.

Procedure: The data collection took place at the University Paul Valéry 3 of Montpellier. Upon gaining authorization from corresponding university authorities and teachers, we used class time to carry out the study. All students who were in class on the day of the assessment participated voluntarily and anonymously in the study. An informed consent was obtained from all participants. First, we evaluated the Brighton criteria for JHS. In this first part, the evaluator (constant for the entire sample), trained for the task by an expert rheumatologist, read a description of each criterion to students and supported the description with illustrative visual material, answering questions and monitoring the correct understanding of the criteria. In the second part of the evaluation, participants completed psychological questionnaires.

Analysis: For data analysis, subjects were divided into two groups: group 1, which included participants who met the Brighton criteria for JHS, and group 2 which included the participants who did not meet the criteria for JHS. Statistical treatment included a descriptive analysis of the data (percentage and average), the Kolmogorov-Smirnov normality test, the chi-square method, the Student's t-test, the Pearson's correlation and binary logistic regression. Data analysis was performed on computer with SPSS 13.0 software package and the significance level was taken as .05 for all statistical tests.

RESULTS

Joint Hypermobility Syndrome: One hundred and forty-four participants (39.5%) met the Brighton criteria for JHS. A significantly higher number of women display JHS than men (18.9% males vs. 44.7% females; $\chi^2 = 16.38$; $p = 0.000$). The most frequent Brighton criteria in the sample were: minor criterion 6: abnormal skin signs such as striae, hyperextensibility, thin skin, atrophic scars (63.3%). Minor criterion 2: arthralgia (= 3 months) in 1 to 3 joints, or back pain (= 3 months), (49%). Minor criterion 1: Beighton score 1, 2, 3 or 4 out of 9 (39.7%). Major criterion 1: Beighton score $\geq$ 5 (joint hypermobility, 38.9%). Minor criterion 4: soft tissue rheumatism (tendonitis, 35.6%) and minor criterion 7: eye signs (myopia, 27.1%).

Correlation between the psychopathological variables: The correlational analysis showed a significant but modest correlation between HADS depression and HADS anxiety ($r=0.34$; $p=0.000$), HADS depression and LSAS total score ($r=0.29$; $p=0.000$), HADS anxiety and somatosensory amplification ($r=0.13$; $p=0.008$), HADS anxiety and LSAS total score ($r=0.33$; $p=0.000$) and somatosensory amplification and LSAS total score ($r=0.14$; $p=0.007$).

Correlation between psychopathological variables and joint hypermobility (Beighton score $\geq$ 5): In men group, we observed a weak positive association between the Beighton score and the LSAS avoidance score ($r=0.26$; $p=0.02$), HADS anxiety score ($r=0.30$; $p=0.008$), and somatosensory amplification score ($r=0.23$; $p=0.04$). No significant correlations have been found between the scores of psychological variables and the Beighton Score in the group of women.

Social anxiety: No significant differences were obtained in LSAS scores between participants with and without JHS (LSAS fear: $t=-1.06$; $p=0.28$. LSAS avoidance: $t=-1.73$; $p=0.08$. LSAS total: $t=-1.45$; $p=0.14$). However, when comparing groups with and without JHS by gender, significant results appear (table 1): men with JHS have higher scores in LSAS avoidance than men without JHS ($t=-2.41$; $p=0.01$), which means that men with JHS avoid in a greater degree the social situations assessed by the LSAS than men without JHS. When the LSAS total score was dichotomized (cut-off score $\geq$30), we observed that the percentage of male participants with a medium/high level of social anxiety was

superior in the case group (78.6% vs. 41.7%; χ^2=6.18; p=0.01). There were no differences in scores between women with and without JHS.

Table 1. Comparison of scores in questionnaires LSAS, HADS and SSAS of participants with and without JHS by gender.

Scale	Male sample N=74		JHS male group n=14		Control male group n=60		*P**	Female sample N=291		JHS female group n=130		Control female group n=161		*P**
	X	SD	X	SD	X	SD		X	SD	X	SD	X	SD	
LSAS fear	14.9	8.8	17.1	7.9	14.4	9	.303	19.7	11.0	19.7	11.4	19.6	10.6	.965
avoidance	15.5	9.8	21	11.5	14.2	9	.018	19.6	11.5	20	12.2	19.4	10.8	.674
total	30.4	17.2	38.2	16.5	28.6	17	.061	39.2	21.2	39.5	22.6	39	20	.833
HADS anxiety	6.8	2.7	6.6	2.8	6.8	2.7	.768	8.5	3.6	9	3.8	8	3.5	.019
depression	4.6	3	5.2	2.8	4.5	3	.462	4.6	2.9	5	3	4.3	2.8	.045
SSAS	24.6	6.1	28	5.2	23.8	6.1	.024	26.0	6.2	26.8	5.8	25.4	6.5	.050

*= Student's t-test. LSAS= Liebowitz Social Anxiety Scale. HADS= Hospital Anxiety and Depression Scale. SSAS= Somatosensory Amplification Scale.

General anxiety: Women with JHS have a higher anxiety score assessed by the HADS than women without JHS (t=-2.35; p=0.019). This result was confirmed when the variable was dichotomized (cut-off score $\geq$11): the percentage of women with a high level of anxiety was superior in the case group (34.6% vs. 23.6%; χ^2=4.27; p=0.03). Men with JHS did not differ from men without the syndrome in anxiety scores.

Depression: We observed that women with JHS showed significantly higher levels of depression as assessed by the HADS than women without JHS (t=-2.01; p=0.045). Men's groups did not differ in the results of this variable (table 1).

Somatosensory amplification: Participants with JHS scored significantly higher in SASS than participants without the syndrome (t =-2.98; p= 0.03). This indicates that students with JHS amplify somatosensory information more than those without JHS. This result was confirmed when comparing groups by gender (Men: t=-2.30; p=0.024. Women: t=-1.97; p=0.050).

To assess the predictive power of psychological variables on the JHS, a logistic regression analysis was performed. Gender, age and all psychological variables that showed association with JHS in bivariate analysis were introduced in the model. As illustrated in table 2, male sex and low score of

somatosensory amplification (≤ 29) are variables contrary to the presence of JHS in this study (Male sex: OR= 0.32; 95%= 0.17-0.62. Low score of SASS: OR=0.55; 95%=0.35-0.88).

Table 2. Logistic regression results for risk of JHS.

variables	B	p	OR	95% IC	
				lower	upper
Age	-.042	.468	.959	.855	1.075
Gender (male)	-1.121	.001	.326	.170	.626
SSAS α (1)	-.582	.013	.559	.353	.885
HADS β anxiety (1)	-.451	.088	.637	.379	1.069
HADS β depression (1)	-.435	.444	.647	.213	1.971
LSAS γ (1)	.039	.872	1.040	.648	1.667

(1)=absence of criteria. α=cut-off score ≥29 in SSAS. β= cut-off score ≥11 in HADS anxiety and depression. γ= cut-off score ≥30 in LSAS.

DISCUSSION

The results of this study show that JHS is a frequent condition (39.5%) among the college students evaluated. Previous studies have reported a high prevalence of JHS using the Brighton criteria, such as Bravo and Wolff [4] who found a prevalence of 39% in rheumatologic cases in Chile, and Grahame and Hakim [34] who report that in the case of non-Caucasian females the figure rises to 58%. According to Grahame [35] the high prevalence found is an unexpected consequence of applying the Brighton criteria to research. This set of criteria published in 2000 by Grahame et al. [27] is the successor instrument that followed the Beighton 9-point criteria [26] for the classification and diagnosis of JHS [3]. Prevalence observed with the Beighton 9-point criteria, ranged from 10 to 15% in western countries [15, 36]; much lower percentages than those obtained with the Brighton criteria. According to Bravo and Wolff [4] the Beighton score is an insufficient method for JHS diagnosis. The differences between these two instruments result from the fact that the Brighton criteria include other signs and symptoms associated with alteration of collagen as well as the joints examined by the Beighton maneuvers. Thus, the Brighton criteria can detect cases of JHS with minimal demonstrable hypermobility [37].

Our results reveal that JHS is much more common in women than in men, as has been widely reported in literature [4, 35, 36]. Therefore, it doesn't surprise that logistic regression analysis showed male sex

as a variable contrary to the presence of JHS. In this regard, female sex hormones have been described as a factor that could influence joint suppleness, such as the relaxin hormone which allows the pelvis to expand so the head of the baby can pass through during delivery [36].

The association between anxiety and JHS described in the literature [7-13] was also observed in this study but with variations according to gender: women with JHS reported higher scores of anxiety according to the HADS questionnaire. Moreover, we observed that men with JHS had higher levels of social anxiety and social avoidance than male participants without the syndrome. In addition, a modest correlation was observed between the Beighton Score for joint hypermobility and the anxiety subscale of the HADS in males. Some authors such as Bulbena [36] consider that anxiety associated with hypermobility appears not to be a secondary response. Findings about a biological shared base between both phenomena support this idea. Concretely, it is an interstitial duplication of human chromosome 15 (named DUP 25) that has been identified as responsible for these associations, which could confirm the heritability (although not strictly Mendelian) of these conditions [16, 36]. However, this finding was not confirmed in subsequent studies [17-19]. Further genetic studies are required, including studies related to psychological variables, to improve our understanding of the association between anxiety and joint hypermobility [13].

Knowledge of the relationship between anxiety and hypermobility offers the opportunity to identify those most vulnerable to anxiety states through the exploration of symptoms and signs of JHS. This is an important contribution considering that anxiety disorders, despite their high prevalence, are often underdiagnosed [7].

In this study, depression levels were higher among female students with JHS than females without JHS. Chronic joint pain has been associated to depression [20, 39]. The presence of any physical symptom of JHS approximately doubled the likelihood that the patient had a mood disorder; the worse the painful physical symptoms, the more severe the depression [39].

To our knowledge, this is the first study which explores the association between somatosensory amplification and JHS. Higher SSAS scores in men and women with JHS revealed that these

participants had a greater tendency to experience somatic and visceral sensations as unusually intense, noxious, and disturbing. Furthermore, logistic regression analysis showed that low level of somatosensory amplification had a protective effect against JHS in this study. Whereas amplification plays a pathogenic role in hypochondriasis [25], our results are consistent with those reported by Ercolani et al. [22], who found more hypochondriasis among patients with JHS as compared to healthy subjects.

This is an interesting contribution of this study, because although JHS has a biological basis for somatic complaints, the perception, recognition and maintenance of these might be influenced by psychological variables such as the tendency to amplify the somatosensory information.

According to Nakao et al. [38], the construct of somatosensory amplification can be useful to explain some of the variability in somatic symptomatology found among different patients with the same medical disorder. Despite the great number of people affected, several people with hypermobility will never notice its presence, and calculations indicate that only one third of them will develop the complete form of JHS [36]. In this regard, it is possible to hypothesize that somatosensory amplification may influence the fact that some people with hypermobility develop JHS and others do not.

One limitation of this study is the cross-sectional design, which simultaneously evaluates psychological variables and the event under study (JHS), precluding any inferences of directionality of relationships. Variables were measured by self-applied questionnaires, and results based on this kind of instrument provide a less reliable measure than an interview; however, this situation was identical for participants with and without JHS. Despite these limitations, our results are consistent with previous findings and they add to the weight of evidence that shows considerable emotional symptoms accompanying JHS. This evidence should not be underestimated by physicians when establishing an integrated biopsychosocial therapy [22].

In conclusion, JHS is a frequent condition among young people evaluated, especially in women. Participants with JHS display the psychopathological factors assessed in this study to a greater extent

than those without JHS. Somatosensory amplification is positively associated with JHS. It is important to disseminate knowledge about psychopathological variables associated with JHS, in order to consider these factors in treatment protocols and to integrate mental health professionals in the overall management of JHS.

Acknowledgements: The authors thank Robert Onus, Hellen Kilgallon, Saul Cabrera and the professors Aude Michel, Oliver Torres, Laure Chantral, Christiane Arnaud and all student volunteers for their valuable collaboration.

Competing interests: The authors declare that they have no competing interests.

REFERENCES

1. Hakim A. Grahame R. Joint Hypermobility. *Best Practice & Research Clinical Rheumatology* 2003; 17: 989-1004.

2. Bravo JF. *Joint hypermobility syndrome: the most frequent cause of pain in rheumatological practice?* Retrieved April 21, 2010, from http://www.medscape.com/viewarticle/537960

3. Grahame R. Pain, distress and joint hyperlaxity. *Joint Bone Spine* 2000; 67:157-163. Grahame R. The need to take a fresh look at criteria for hypermobility. *The Journal of Rheumatology* 2007; 34:664-665.

4. Bravo J, Wolff C. Clinical study of hereditary disorders of connective tissues in a Chilean population: joint hypermobility syndrome and vascular Ehlers-Danlos syndrome. *Arthritis and Rheumatism* 2006; 54:515-23.

5. Gumà M, Olivé A, Holgado S, Casado E, Roca J, Forcada J, et al. Una estimación de la laxitud en la consulta externa. *Revista Española de Reumatología* 2001; 28:298-300.

6. Watson D, Clark LA, Weber K, Assenheimer JC, Strauss ME, McCormick RA. Testing a tripartite model: II. Exploring the symptom structure of anxiety and depression in student, adult, and patient samples. *Journal of Abnormal Psychology* 1995, 104, 15-25.

7. Baeza-Velasco C. Bulbena A. The relationship between anxiety and joint hypermobility: Literature review. *Annales Médico Psychologiques* 2010; 168:263-267.

8. Martín-Santos R, Bulbena A, Porta M, Gago J, Molina L, Duró J. Association between joint hypermobility syndrome and panic disorder. *American Journal of Psychiatry* 1998; 155:1578-1583.

9. Bulbena A, Duro´ J, Mateo A, Porta M, Vallejo J. Joint hypermobility syndrome and anxiety disorders (letter). *Lancet* 1988; 2:694.

10. Bulbena A, Gago J, Sperry L. Berge D. The relationship between frequency and intensity of fears and collagen condition. *Depression and Anxiety* 2006; 23:412–7.

11. Gülsün M, Doruk A, Uzun O, Tonbul M. Eklem hipermobilite sendromu olan klinic disi erkek örnekleminde anksiyete bozukluklari. *Yeni Symposium Journal* 2006; 44, 165–8.

12. Gülsün M, Yilmaz MB, Pinar M, Tonbul M, Celik C, Ozdemir B, et al. Thorax deformity, joint hypermobility and anxiety disorders. *Saudi Medical Journal* 2007; 28:1840-4.

13. Baeza-Velasco C, Bulbena A, Bravo JF. Anxious symptomatology and Joint Hypermobility Syndrome (JHS) in a group of Chilean undergraduate students. *Ansiedad y Estrés* 2010; 16:1-

14. Gago J. *Estudio de Prevalencias y Asociación de Laxitud Articular y Trastornos Ansiosos-Fóbicos en el medio Rural*. Tesis doctoral. Facultad de Medicina, Universidad Autónoma de Barcelona, 1992.

15. Baeza-Velasco C, Bulbena A. Social anxiety and collagen-altering condition in high stature people. *Cuadernos de Medicina Psicosomática y Psiquiatría de Enlace* 2009; 89/90:40-46.

16. Gratacòs M, Nadal M, Martín-Santos R, Pujana MA, Gago J, Peral B, et al. A polymorphic genomic duplication on human chromosome 15 is a susceptibility factor for panic and phobic disorders. *Cell* 2001; 106:367–379.

17. Neergaard-Henrichsen C, Delorme R, Boucherie M, Marelli D, Baud P, Bellivier F. et al. No association between DUP25 and anxiety disorders. *American Journal of Medical Genetics* Part B Neuropsychiatric Genetics 2004; 128;80–83.

18. Schumacher J, Otte A, Becker T, Sun Y, Wienker T, Wirth B. et al. No evidence for DUP25 in patients with panic disorder using a quantitative real-time PCR approach. *Human Genetics* 2003; 114:115–117.

19. Tabiner M, Youings S, Dennis N, Baldwin D, Buis C, Mayers A. et al. Failure to find DUP25 in patients with anxiety disorders, in control individuals, or in previously reported positive control cell lines. *American Journal of Human Genetics* 2003; 72:535–538.

20. Lumley M, Jordan M, Rubenstein R, Tsipouras P, Evans M. Psychosocial functioning in the Ehlers-Danlos syndrome. *American Journal of Medical Genetics* 2005; 53:149-152.

21. Fishbain D, Cutler R, Rosomoff H, Rosomoff R. Chronic pain-associated depression: antecedent or consequence of chronic pain? A review. *The Clinical Journal of Pain* 1997; 13:116-137.

22. Ercolani M, Galvani M, Franchini C, Baracchini F, Chattat R: Bening joint hypermobility syndrome: Psychological features and psychopathological symptoms in a sample pain-free at evaluation. *Perceptual and Motor Skills* 2008; 107:246-256.

23. Barsky AJ, Goodson JD. Lane RS. Cleary PD. The amplification of somatic symptoms. *Psychosomatic Medicine* 1988; 50:510-519.

24. Barsky AJ. Amplification, somatization, and the somatoform disorders. *Psychosomatics* 1992; 33:28-34.

25. Belloch A, Ayllón E, Martínez MP, Castañeiras C, Jiménez, MA. Sensibilidad a las sensaciones corporales e hipocondría. *Revista de Psicopatología y Psicología Clínica* 1999; 4:1-14.

26. Beighton PH, Solomon L, Soskolne CL. Articular mobility in an African population. *Annals of the Rheumatic Disease* 1973; 32:413-7.

27. Grahame R, Bird HA, Child A, et al. The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). *Journal of Rheumatology* 2000; 27:1777-1779.

28. Zigmond A. Snaith R. The Hospital Anxiety and Depresión Scale. *Acta de Psiquiatría Escandinava* 1983; 67:361-370.

29. Lépine JP, Godchau M, Brun P, Lemperière T. Evaluation de l'anxiété et de la dépression chez des patients hospitalisés dans un service de médecine interne. *Annales Médico Psychologiques* 1985 ; 143 :175-89.

30. Liebowitz M. *Social Phobia*. In D. F. Klein (Ed.), Anxiety (pp. 141-173). Karger, New York, 1987.

31. Yao SN, Note I, Fanget F, Albuisson E, Bouvard M, Jalenques I, Cottraux J. Social anxiety in patients with social phobia: validation of the Liebowitz Social Anxiety Scale: the French version. *L'Encéphale* 1999; 25:429-435.

32. Barsky AJ, Wyshak G, Klerman GL. The somatosensory amplification scale and its relationship to hypochondriasis. *Journal of Psychiatric Research* 1990; 24: 323–4.

33. Bridou M, Aguerre C. *Qualités psychométriques de la version française de l'échelle d'amplification somatosensorielle de Barsky*. Congress of the French Psychological Society (SFP), Bordeaux, Sept. 2008.

34. Grahame R, Hakim AJ. High prevalence of joint hypermobility syndrome in clinic referrals to a north London community hospital. *Rheumatology* 2004; 43(Supp 2):91

35. Grahame R. The need to take a fresh look at criteria for hypermobility. *The Journal of Rheumatology* 2007; 34:664-665.

36. Bulbena A, Benito P, Pailhez G, Gago J, Carbonell J, Sperry L. *Hiperlaxitud Articular, definición y exploración*. Programa interactivo de formación (Cd room). Barcelona: Institut d'Atenció Psiquiàtrica Salud Mental i Toxicomanies Hospital del Mar, Barcelona, 2004.

37. Menéndez F. De la laxitud a la hipermovilidad articular. *Revista Cubana de Reumatología* 2005; 7:7-8.

38. Nakao M, Barsky AJ, Kumano H, Kuboki T. Relationship between somatosensory amplification and alexithymia in a Japanese psychosomatic clinic. *Psychosomatics* 2002; 43:55-60.

39. Trivedi MH. The link between depression and physical symptoms. *Prim Care Companion J Clin Psychiatry* 2004; 6[suppl 1]:12–16.