Curr Psychiatry Rep
DOI 10.1007/s11920-010-0164-0

Joint Hypermobility and Anxiety: The State of the Art

Javier Garcia-Campayo · Elena Asso · Marta Alda

Abstract Joint hypermobility (JH) is considered a common benign, hereditary, overlap, connective tissue disorder with a prevalence in the general population of about 10% in European populations and 25% in other ethnic groups. JH shows an association with mitral valve prolapse and fibromyalgia. However, the most significant and important association between joint hypermobility syndrome (JHS) and any other disorder from a clinical point of view is with panic disorder. This article summarizes all published studies on JHS and anxiety, analyzing the main results and limitations. An overview of the etiologic explanation of the association between JH and anxiety, with special focus on genetic findings, is also included. The most relevant conclusions are the following: JHS is more prevalent in individuals with panic disorder/agoraphobia, and patients with JHS present with greater prevalence of panic disorder/agoraphobia. In addition, there is an association between JHS severity and severity of anxiety, and mitral valve prolapse plays a secondary role in the association between JHS and anxiety. New fields of research based on these data are suggested.

Keywords Joint hypermobility · Anxiety · Association · Mitral valve prolapse

J. Garcia-Campayo (✉) · E. Asso · M. Alda
Department of Psychiatry, Miguel Servet University Hospital, Aragonese Institute of Health Sciences, University of Zaragoza, Avenida Gomez Laguna 52, 4D, 50.009 Zaragoza, Spain
e-mail: jgarcamp@arrakis.es

Introduction

Joint hypermobility (JH) is a highly heritable clinical condition characterized by an increased distensibility of joints in passive movements, and hypermobility in active movement in the absence of a systemic rheumatologic disease [1]. It is considered a common benign, hereditary, overlap, connective tissue disorder that incorporates many of the classic features seen in other major connective tissue disorders, such as Marfan and Ehlers-Danlos syndromes and osteogenesis imperfecta. Joint hypermobility syndrome (JHS) often goes unnoticed, but patients with JHS usually present with traumatic or overuse soft tissue lesions, recurrent joint dislocation or subluxation, arthralgia, or low-grade inflammatory or degenerative arthritis [1].

The first study on this disorder was carried out in soldiers during their military service in 1947 [2]. The term *joint hypermobility syndrome* was used for the first time in 1967 to describe the association of this condition with some musculoskeletal diseases [3]. The prevalence of JHS in the general population seems to range between 10% in European populations and 25% in other ethnic groups [4], with laxity being more frequent in Asians than in Africans and more so in Europeans. It is more common in women than men (3:1 ratio) [1]. By age group, it is more common among children and adolescents, with its frequency decreasing with age. Prevalence of JHS decreases in men in the third decade and in women in the fifth decade of life [5].

Carter and Wilkinson [6] were the first authors to define the operative criteria to diagnose JHS. In 1973, Beighton et al. [7] modified these criteria to carry out an epidemiologic study. These criteria include five tests that can be assessed on a nine-point scale, with patients scoring five or higher considered to suffer from JHS. Since then, this has become

Published online: 21 October 2010

the most commonly used system to diagnose JHS, despite other subsequent diagnostic criteria being proposed to improve diagnosis in specific patient gender and age subgroups. JHS is associated with articular and extra-articular symptoms. The most common articular symptoms are flat feet, deviations of knee axes (genu varum and genu valgum), scoliosis, kyphosis, hyperlordosis, recurrent luxations and subluxations, temporomandibular joint dysfunction, spontaneous torticollis, epicondylitis, carpal tunnel syndrome, and ankle sprain [8]. With regard to extra-articular JHS symptoms, the following should be highlighted as the most important: ecchymosis, hemorrhages and peripheric circulatory phenomena (e.g., Raynaud's phenomenon), aneurysm rupture, spontaneous pneumothorax, diverticulosis, hydronephrosis, hernias (inguinal, umbilical, and crural), vaginal and uterine prolapses, and myopia [9–11]. The asthenic somatotype has also been related, with a higher rate being shown in patients with panic disorder and agoraphobia than in psychiatric or medical comparison individuals [12].

Some studies confirm that JHS can produce rheumatologic complications such as premature osteoarthrosis, calcium pyrophosphate crystal deposition, and chondrocalcinosis [13–15]. Other studies show an association between JHS and fibromyalgia, with the prevalence of JHS in patients with fibromyalgia ranging between 25% [16•] and 27% [17].

In addition, a significant association between JHS and mitral valve prolapse (MVP) has been described [18, 19] despite some controlled studies that have failed to detect this association [9]. MVP is the most common abnormality of the heart valves in industrialized nations, affecting 3% or more of the adult population [20]. Curiously, a bidirectional association between MVP and panic disorder has been detected [21, 22]. A meta-analysis of empiric studies on this subject demonstrated a significant association between the two (OR, 2.3) [23].

Joint Hypermobility Syndrome–Anxiety Association

The most significant and important association between JHS and other disorders from a clinical point of view is with panic disorder. All published studies on JHS and anxiety are described subsequently and summarized in Table 1.

This association was referred to for the first time in 1988 in a letter to the *Lancet* by Bulbena et al. [24] from Barcelona, Spain. It was a preliminary case-control study (112 JHS cases and 50 controls) that was thoroughly described in a 1993 article [25]. This definitive research included 114 patients with JHS and 59 randomly selected controls from the same rheumatology outpatient clinic. Results in both studies were the same: there was a significant association between JHS and panic disorder/agoraphobia (OR, 4.12) and simple phobia (OR, 3.03), with an age- and sex-adjusted OR of 10.7. However, no association was found between JHS and generalized anxiety disorder, major depressive disorder, or dysthymia [24, 25]. In this study, MVP was present only among individuals with JHS. Among the cases of JHS, individuals with MVP were almost three times more likely to suffer from anxiety than those without MVP (OR, 2.95), although this association was not statistically significant [24, 25].

The Bulbena group (Martín-Santos et al. [26]) carried out a new study in 1998. In this case, the sample consisted of 99 untreated patients newly diagnosed with panic disorder, agoraphobia, or both who were recruited at the outpatient clinic of a general teaching hospital, except for medical controls, who were recruited from four medical outpatient clinics. There were two control groups: 1) psychiatric patients (whose specific psychiatric diagnosis is not described in the article [n=99]) and 2) medical patients (n=64) with no previous history of anxiety. Prevalence of JHS was significantly higher in those with panic/agoraphobia (67.7%) compared with psychiatric patients (10.1%) or medical controls (12.5%). In this article, patients with anxiety were more likely to suffer from JHS than were the psychiatric and medical controls (OR compared with psychiatric controls, 18.6; OR compared with medical controls, 14.7). The magnitude of the association suggests a causal JHS–panic/agoraphobia connection, but the direction is unclear. It is unusual in clinical settings to find patients with panic/agoraphobia who do not also suffer from JHS. The opposite, JHS preceding panic, is more common because JHS is present from early childhood.

Finally, this same group (Bulbena et al. [27]) carried out a new study in 2004 on the relationship between JHS and anxiety (trait and state anxiety) in a group of nonclinical individuals. The patients were recruited from the medical department of a large auditing consultancy and legal services company in Barcelona, Spain, in which all workers are periodically examined during a routine medical check-up. The sample (N=526) was made up of all those who attended the medical office consecutively over 4 months, ruling out patients suffering from joint conditions that could hamper the examination for JHS, and those suffering from anxiety disorders or being treated with antianxiety drugs. Women with JHS showed significantly higher trait anxiety than did nonhypermobile women (median scores, 17 and 11, respectively; P<0.001). The difference in state anxiety was not significant (13 vs. 12; P=0.30). Among the men, those with JHS also showed significantly higher trait anxiety scores (median, 13) than nonhypermobile men (median, 11; P<0.05), whereas the difference in median

Table 1 Research studies on JHS and anxiety

Study (year)	Design	Setting	Sample	Main results	Comments
Bulbena et al. [24] (1988); Bulbena et al. [25] (1993)	Case-control study	Rheumatology outpatient clinic	114 patients with JHS, 59 controls randomly selected from the same clinic	Significant association between JHS and panic disorder/agoraphobia, simple phobia	First study demonstrating that patients with JHS present more frequently with panic disorder/agoraphobia
				No association between JHS and generalized anxiety disorder	JHS patients with MVP do not present with more anxiety
Martín-Santos et al. [26] (1998)	Case-control study	General teaching hospital outpatient clinic (except medical controls recruited from 4 medical outpatient clinics)	99 untreated, newly diagnosed patients with panic disorder, agoraphobia, or both; 99 psychiatric controls; and 64 medical patient controls with no previous history of anxiety	Prevalence of JHS is significantly higher in patients with panic disorder/agoraphobia compared with psychiatric patients or medical controls	First study demonstrating that patients with panic disorder/agoraphobia present more frequently with JHS
				Presence of MVP in panic disorder/agoraphobia patients did not modify this association	MVP plays a secondary role in the association between JHS and panic disorder/agoraphobia
					Magnitude of the association suggests a causal JHS–panic disorder/agoraphobia connection, but the direction is unclear
Bulbena et al. [27] (2004)	Prevalence study	Medical department of a large auditing consultancy and legal services company	526 patients who attended the medical office consecutively over 4 mo, ruling out patients suffering from joint conditions that could hamper the examination for JHS and those suffering from anxiety disorders or treated with antianxiety drugs	Women and men with JHS showed significantly higher trait anxiety than nonhypermobile individuals, whereas there were no differences in state anxiety scores	First article to confirm significantly more anxiety in healthy people with JHS, and significant correlation between anxiety and JHS in this population
				Both trait and state anxiety showed modest but significant correlations with JHS	JHS was assessed using Hospital del Mar criteria (Beighton criteria were used in all other articles)
Benjamin et al. [28] (2001)	Case-control study	University medical school psychiatry department	101 patients with panic disorder, 39 healthy volunteers	Rate of hyperlax joints did not differ among patients with panic disorder compared with healthy volunteers	Replication study of research by Martín-Santos et al. [26]
				No associations between responses to carbon dioxide and hyperlaxity	Instruments to assess anxiety (National Institute of Mental Health self-rating scale, *DSM-IV* panic symptom scores, and 100-mm visual analogue scales of anxiety) were unusual in these studies and could explain no differences between patients with panic disorder and controls
					First study to demonstrate no association between responses to carbon dioxide and hyperlaxity

Table 1 (continued)

Study (year)	Design	Setting	Sample	Main results	Comments
Gulpek et al. [29] (2004)	Case-control study	University medical school psychiatry department	Sample was made up of 115 individuals divided into 3 groups: group 1 (n=42), consisting of patients with panic disorder with MVP; group 2 (n=35), consisting of patients with panic disorder without MVP; and group 3 (n=38), consisting of controls with MVP but without any psychiatric illness	No significant difference between groups in prevalence or severity of JHS, according to Beighton scores Study suggests that MVP affects the prevalence of JHS in panic disorder patients	Replication study of research by Martín-Santos et al. [26] Prevalence of JHS (52.6%) in the control group was unbelievably high; this could explain the absence of significant differences compared with the panic disorder group
Gülsün et al. [30] (2006)	Case-control study	No data	No data	Prevalence of panic disorder in patients with JHS significantly higher than among controls	Replication study of research by Martín-Santos et al. [26]
Garcia-Campayo et al. [16•] (2010)	Case-control study	Primary care settings	Sample was made up of 220 patients divided into 4 groups: group 1 (n=55), newly diagnosed and untreated patients with panic disorder; group 2 (n=55), a psychiatric control group (newly diagnosed psychiatric patients who did not suffer from *DSM-IV* panic disorder); group 3 (n=55), a fibromyalgia control group; and group 4 (n=55), a healthy control group	Prevalence of JHS in panic disorder was 61.8% vs. 10.9% in healthy controls (OR, 13.2), and 9% in psychiatric controls (OR, 16.1) Significant correlation between the number of Beighton criteria and PAS scoring, but not with State-Trait Anxiety Inventory or Hamilton Anxiety and Depression Scale	Replication study of research by Martín-Santos et al. [26] and Bulbena et al. [27] Patients with panic disorder present more frequently with JHS JHS correlates with panic disorder but not with nonspecific anxiety

JHS joint hypermobility syndrome, *MVP* mitral valve prolapse, *PAS* panic and agoraphobia scale

state anxiety scores (12 vs. 11, respectively) was not achieved (P=0.053). Both trait and state anxiety showed modest but significant correlations (Spearman's rho, 0.10–0.16; P<0.05) with JH.

To our knowledge, there have been only four replication studies of the Bulbena group research published, with inconclusive results. The first was carried out in 2001 by Benjamin et al. [28] at a university medical school psychiatry department in Israel. The sample was made up of 101 patients with panic disorder and 39 healthy volunteers. This study attempted to replicate the associations between panic disorder and JHS (i.e., a replication of the Martín-Santos et al. [26] study). In addition, the authors examined possible associations between reactivity to carbon dioxide, a model for panic vulnerability, and hyperlaxity in healthy volunteers. Thirteen (13%) patients had five or more hyperlax joints. This rate did not differ from that among the healthy volunteers. Anxiety in healthy volunteers, as measured by the National Institute of Mental Health self-rating scale, *DSM-IV* panic symptom scores, and 100-mm visual analogue scales of anxiety, increased after carbon dioxide from a mean of 1.8–2.8 (not significant); from 0.5 to 4 (P<0.001); and from 8.7 to 11.6 mm (P<0.1), respectively. No associations were noted between responses to carbon dioxide and hyperlaxity.

The second study was developed in Turkey in 2004 [29]. Its purpose was to test the association between JHS and panic disorder and to determine whether MVP modifies or accounts in part for this association. Therefore, it was a replication of the 1998 study by Martín-Santos et al. [26]. This was a case-control study developed at a university medical school psychiatry department. The sample was made up of 115 individuals divided into three groups: group 1 (n=42), consisting of panic disorder patients with MVP; group 2 (n=35), consisting of panic disorder patients without MVP; and group 3 (n=38), consisting of controls who had MVP without psychiatric illness. In this study, JHS was found in 59.5% of panic disorder patients with MVP, in 42.9% of patients without MVP, and in 52.6% of controls. No significant difference was found among the groups with regard to prevalence of JHS or severity of JHS, according to Beighton scores. The study suggests that MVP affects the prevalence of JHS in panic disorder patients.

The third study—the only one to confirm the association between panic disorder and JHS—has only been published in Turkish [30]. We have no information on the characteristics of the sample and the setting in which participants were recruited. The only information we have is that the prevalence of panic disorder in patients with JHS is significantly higher than in controls.

The fourth study was conducted in Spain in 2010 [16•]. This was a case-control study carried out in primary care settings. Sample size was 220 patients divided into 4 groups: group 1 (n=55), consisting of panic disorder (newly diagnosed and untreated patients with panic disorder); group 2 (n=55), a psychiatric control group (newly diagnosed psychiatric patients who did not suffer from *DSM–IV* panic disorder and who had never met criteria for any anxiety disorder); group 3 (n=55), a fibromyalgia control group; and group 4 (n=55), a healthy control group. The main results of this study were as follows: the prevalence of JHS, according to Beighton's criteria, in those with panic disorder was 61.8%, which was significantly higher than the 10.9% observed in healthy controls (OR, 13.2) and the 9% observed in the psychiatric control group (OR, 16.1). There is a significant correlation between the number of Beighton criteria and Panic and Agoraphobia Scale scoring, but not with the other tests of anxiety used (State-Trait Anxiety Inventory, Hamilton Anxiety and Depression Scale). Among patients with panic disorder, the subgroup with JHS was younger, and their Panic and Agoraphobia Scale scores were higher than in patients with panic disorder without JHS. From a clinical point of view, the only difference between these two groups were that panic patients with JHS presented "trembling or shaking" and "chills or hot flashes" more frequently than the group without JHS. However, the total number and severity of panic symptoms and the patients' age at onset of the disorder were similar.

Genetic Studies on the Association Between Joint Hypermobility Syndrome and Anxiety

In 2001, the Bulbena group (Gratacòs et al. [31]) identified an interstitial duplication of human chromosome 15q24-26 (DUP25) that was significantly associated with panic/agoraphobia/social phobia/joint laxity in families, and with panic disorder in nonfamilial cases. Mosaicism, different forms of DUP25 within the same family, absence of segregation of 15q24-26 markers with DUP25, and the psychiatric phenotypes suggest a nonmendelian mechanism of disease-causing mutation. These authors proposed that DUP25, which was present in 7% of the controls, is a susceptibility factor for a clinical phenotype that includes panic and phobic disorders and JHS [31].

However, this genetic finding was not confirmed by two other research groups, which achieved negative results in 2003 [32, 33]. No other research has been carried out in this field to date.

Etiologic Explanation for the Joint Hypermobility Syndrome–Anxiety Association

Some authors, such as Roy-Byrne et al. [34•], have described the consistent relationship between anxiety

disorders and comorbid medical illness, which is as common as the association between depression and medical illness. They summarize biological theories of the interactions between anxiety and irritable bowel syndrome, cardiovascular diseases, and chronic pain [34•]. We also have noted that the most prevalent psychiatric disorders in primary care are affective (35.8%), anxiety (25.6%), and somatoform (28.8%) disorders, and that 11.5% of patients in this setting present with comorbidity among affective, anxiety, and somatoform disorders [35]. In addition, we have even confirmed that intervention programs for the prevention of somatoform disorders decrease the prevalence of anxiety and depressive disorders at 5-year follow-up [36]. The conclusion is that the overlap among anxiety, depression, and somatic symptoms is so prevalent and consistent that it should be taken into account in psychiatric classifications [35].

However, the Bulbena group (Pailhez et al. [37•]) believes that most of the conditions referred to as being associated with anxiety disorders (i.e., irritable bowel syndrome, cardiovascular disease, asthma, and chronic pain) can be explained as clinical features of JHS. They consider that there are various hypotheses on how medical illness and anxiety disorders may be related. Obviously, the simplest explanation is that medical illness or its treatment may directly cause anxiety (e.g., hyperthyroidism), trigger anxiety symptoms (e.g., a negative coping with the illness), or worsen some somatic conditions (e.g., gastric ulcer). However, for the Bulbena group, there is enough evidence to show that some medical conditions that are often comorbid with anxiety disorders could share a common genetic etiology [38]. They refer to a recent family study that found that panic or social anxiety patients and their first-degree relatives were more likely to have interstitial cystitis, MVP, and headaches, which was hypothesized to be linked to a common genetic susceptibility [39•]. JHS is accepted as a heritable connective tissue disorder (Ehlers-Danlos syndrome, probably type III) associated with a generalized collagen laxity and characterized by an increase in active or passive joint mobility [40]. It has been demonstrated that JHS and anxiety disorders have a similar prevalence in the general population—between 10% and 15%—and with a similar female predominance (3:1), and that many somatic symptoms associated with JHS (arthralgia, headaches, asthma, increased incidence of cardiac [e.g., MVP or high elasticity of the aortic wall] and digestive problems [reflux, irritable bowel syndrome, and diverticulosis]) and the so-called functional illnesses, such as fibromyalgia, temporomandibular joint disorder, and chronic fatigue, are also common in individuals with anxiety. These data lead some authors to defend the notion that comorbid medical disorders found in anxiety are really associated with JHS, and secondary to a connective tissue disorder [37•]. Consequently, several authors suggest that clinicians should assess the existence of medical conditions, including JHS, in anxiety patients.

Another relevant question is how to explain different levels of severity of anxiety related to JHS severity. A dimensional model could explain this relationship. JHS could be linked to innate forms of excessive response to fear [41, 42] or behavioral inhibition [43] that, along with rearing factors, would develop as symptoms of different degrees of severity. Contrary to this is evidence that the experience of extreme fear is different [44]; therefore, a simple continuum is unclear. At any rate, given the present state of knowledge, joining the different pieces of this puzzle will be a difficult task.

Limitations of These Studies

The two main limitations—certainly minor ones—that we have found regarding the studies assessing the relationship between JHS and anxiety are the following.

Different Diagnostic Criteria for Hyperlaxity

As we have described, the Beighton criteria are the most widely acknowledged and used on an international level [7]. However, in a subsequent study of the validity and reliability of different JHS criteria, a widening of Beighton's criteria to improve detection in men was proposed, and these criteria were called *Hospital del Mar* criteria [45]. Grahame [46] also proposed a new set of criteria, including extra-articular symptoms, for better detection of the

Table 2 Assessments still needed from multicenter, community-based, epidemiologic studies with large samples

The effect of sociodemographic variables and anxiolytic medication intake on the JHS–panic disorder association
The existence of a gradient between JHS and anxiety (more JHS symptoms, more anxiety symptoms, and vice versa)
The association between JHS and other anxiety disorders (e.g., generalized anxiety disorder, phobias, or obsessive-compulsive disorder)
The effect of mitral valve prolapse on JHS–anxiety comorbidity
The association of JHS–anxiety comorbidity with other connective tissue disorders
The role of genetic findings such as DUP25 in JHS–anxiety comorbidity

JHS joint hypermobility syndrome

condition regardless of gender or age. This new definition is broader and includes patients who would not be included under the previous criteria. In summary, diagnosis of JHS is clinical. Different diagnostic criteria exist, and the reliability of the diagnosis is limited. Therefore, conclusions on the etiology or other characteristics of JHS should be considered with caution. In addition, as seen in Table 1, despite most of the studies using the Beighton criteria, one of them used the Hospital del Mar criteria [27]; thus, the results are not exactly comparable.

Different Recruitment Settings

The patients in these studies were recruited in different environments, such as primary care settings [16•], psychiatry departments [28, 29], rheumatology clinics [24, 25], general teaching hospital outpatient clinics [26], and a legal services company [27]. For these reasons, their results are not exactly comparable, and the external validity of most of the studies is rather limited. It is also possible that these patients are not representative of those found in the community.

Conclusions and New Fields of Research

As a result of our review, we can conclude with the statements that we have summarized in Table 2.

In conclusion, it seems clear that patients with JHS are more anxious than those without JHS. As a result, new biological cues for fear, conditioning, and panic could be pursued, and integrative models for fear (innate vs. acquired) and anxiety might be built. The role of connective tissue disorders in this association also must be clarified.

Disclosure No potential conflicts of interest relevant to this article were reported.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Beighton PH, Grahame R, Bird H: Hypermobility of Joints, edn 2. London: Springer-Verlag; 1989.
2. Sutro J: Hypermobility of knees due to overlengthed capsular and ligamentous tissues. Surgery 1947, 21:67–76.
3. Kirk JH, Ansell B, Bywaters EGL: The hypermobility syndrome. Ann Rheum Dis 1967, 26:419–425.
4. Grahame R: Hypermobility syndrome. In Rheumatology, vol II, edn 2. Edited by Kipplel JH, Dieppe PA. London: Mosby; 1997:1–6.
5. Winne-Davies R: Familial joint laxity. Proc R Soc Med 1971, 64:689.
6. Carter C, Wilkinson J: Persistent joint laxity and congenital dislocation of the hip. J Bone Joint Surg 1964, 46:40–45.
7. Beighton PH, Solomon L, Soskolne CL: Articular mobility in an African population. Ann Rheum Dis 1973, 32:413–418.
8. De Coster PJ, Van den Berghe LI, Martens LC: Generalized joint hypermobility and temporomandibular disorders: inherited connective tissue disease as a model with maximum expression. J Orofac Pain 2005, 19:47–57.
9. Mishra MB, Ryan P, Atkinson P, et al.: Extra-articular features of benign joint hypermobility syndrome. Br J Rheumatol 1996, 35:861–866.
10. Bird HA: Articular and tissue laxity. Rheumatol Rev Rep 1984, 4:11–22.
11. Al-Rawi Z, Al-Rawi Z: Joint hypermobility in women with genital prolapse. Lancet 1982, i:1439–1441.
12. Bulbena A, Martín-Santos R, Porta M, et al.: Somatotype in panic patients. Anxiety 1996, 2:80–85.
13. Bird HA, Tribe CR, Bacon PA: Joint hypermobility leading to osteoarthrosis and chondrocalcinosis. Ann Rheum Dis 1978, 37:203–211.
14. Bridges AJ, Smith E, Reid J: Joint hypermobility in adults referred to rheumatologic clinics. Ann Rheum Dis 1992, 51:793–796.
15. Gulbahar S, Sahin E, Baydar M, et al.: Hypermobility syndrome increase the risk for low bone mass. Clin Rheumatol 2005, 26:1–4.
16. • Garcia-Campayo J, Asso E, Alda M, et al.: Association between joint hypermobility syndrome and panic disorder: a case-control study. Psychosomatics 2010, 51:55–61. *The most recent study on the subject confirmed a higher prevalence of JHS in patients with panic disorder and the association of severity symptoms between anxiety and JHS.*
17. Acasuso-Diaz M, Collantes-Estevez E: Joint hypermobility in patients with fibromyalgia syndrome. Arthritis Care Res 1998, 11:39–42.
18. Grahame R, Edwards JC, Pitcher D, et al.: A clinical and echocardiographic study of patients with hypermobility syndrome. Ann Rheum Dis 1981, 40:541–546.
19. Pitcher D, Grahame R: Mitral valve prolapse and joint hypermobility: evidence for systemic connective tissue abnormality? Ann Rheum Dis 1982, 41:352–354.
20. Devereux RB: Recent developments in the diagnosis and management of mitral valve prolapse. Curr Opin Cardiol 1995, 10:107–116.
21. Alpert MA, Sabati M, Kushner MG, et al.: Frequency of isolated panic attacks and panic disorder in mitral valve prolapse syndrome. Am J Cardiol 1992, 69:1489–1490.
22. Sivaramakrishnan K, Alexander PJ, Saharsamaman N: Prevalence of panic disorder in mitral valve prolapse: a comparative study. Acta Psychiatr Scand 1994, 89:59–61.
23. Katerndahl DA: Panic and prolapse: meta-analysis. J Nerv Ment Dis 1993, 181:539–544.
24. Bulbena A, Duro JC, Porta M, Vallejo J: Anxiety disorders in the joint hypermobility syndrome. Lancet 1988, 2:694.
25. Bulbena A, Duró JC, Porta M, et al.: Anxiety disorder in the joint hypermobility syndrome. Psychiatry Res 1993, 43:59–68.
26. Martín-Santos R, Bulbena A, Porta M, Molina LI: Association between joint hypermobility syndrome and panic disorder. Am J Psychiatry 1998, 155:1578–1583.
27. Bulbena A, Agulló A, Pailhez G, et al.: Is joint hypermobility related to anxiety in a non-clinical population also? Psychosomatics 2004, 45:432–437.
28. Benjamin J, Ben-Zion IZ, Dannon P, et al.: Lack of association between joint hyperlaxity and I: panic disorder, and II: reactivity to carbon dioxide in healthy volunteers. Hum Psychopharmacol 2001, 16:189–192.

29. Gulpek D, Bayraktar E, Akbay SP, et al.: Joint hypermobility syndrome and mitral valve prolapse in panic disorder. Prog Neuropsychopharmacol Biol Psychiatry 2004, 28:969–973.
30. Gülsün M, Doruk A, Uzun Ö, et al.: Hipermobilite sendromu olan klinik disi erkek Ö rnekleminde anksiyete bozukluklari [in Turkish]. Yeni Symp J 2006, 44:165–168.
31. Gratacòs M, Nadal M, Martin-Santos R, et al.: A polymorphic genomic duplication on human chromosome 15 is a susceptibility factor for panic and phobic disorders. Cell 2001, 106:367–379.
32. Tabiner M, Youings S, Dennis N, et al.: Failure to find DUP25 in patients with anxiety disorders, in control individuals, or in previously reported positive control cell lines. Am J Hum Genet 2003, 72:535–538.
33. Weiland Y, Kraus J, Speicher MR: A multiclot FISH assay does not detect DUP25 in control individuals or in reported positive control cells. Am J Hum Genet 2003, 72:1349–1352.
34. • Roy-Byrne PP, Davidson KW, Kessler RC, et al.: Anxiety disorders and comorbid medical illness. Gen Hosp Psychiatry 2008, 30:208–225. *This recent review describes the many physical symptoms that can accompany anxiety and the long list of medical disorders than can explain them.*
35. Roca M, Gili M, Garcia-Garcia M, et al.: Prevalence and comorbidity of common mental disorders in primary care. J Affect Disord 2009, 119:52–58.
36. García-Campayo J, Arevalo E, Claraco LM, et al.: A prevention programme for somatoform disorders is effective for affective disorders. J Affect Disord 2010, 122:124–132.
37. • Pailhez G, Bulbena A, Fullana MA, Castaño J: Anxiety disorders and joint hypermobility syndrome: the role of collagen tissue. Gen Hosp Psychiatry 2009, 31:299. *This short letter emphasizes that most medical symptoms presented by patients with anxiety could be explained by a collagen tissue disorder such as JHS.*
38. Gratacòs M, Nadal M, Martín-Santos R, et al.: A polymorphic genomic duplication on human chromosome 15 is a susceptibility factor for panic and phobic disorders. Cell 2001, 106:367–379.
39. • Talati A, Ponniah K, Strug LJ, et al.: Panic disorder, social anxiety disorder, and a possible medical syndrome previously linked to chromosome 13. Biol Psychiatry 2008, 63:594–601. *This study confirmed that patients with panic disorder or social anxiety disorder, as compared with controls, reported significantly more interstitial cystitis and MVP. First-degree relatives of probands with panic disorder or social anxiety disorder were also at increased risk of interstitial cystitis, MVP, thyroid problems, and headaches, regardless of whether the proband reported the same condition.*
40. Keer R, Grahame R: Hypermobility Syndrome. New York: Butterworth Heinemann; 2003.
41. Davis M: Neurobiology of fear responses: the role of the amygdala. J Neuropsychiatry Clin Neurosci 1997, 9:382–402.
42. Grove G, Coplan JD, Hollander E: The neuroanatomy of 5-HT dysregulation and panic disorder. J Neuropsychiatry Clin Neurosci 1997, 9:198–208.
43. Rosenbaum JF, Biederman J, Hirshfeld DR, et al.: Behavioral inhibition in children: a possible precursor to panic disorder or social phobia. J Clin Psychiatry 1991; 52(Suppl 11):5–9.
44. Klein DF: False suffocation alarms, spontaneous panics, and related conditions: an integrative hypothesis. Arch Gen Psychiatry 1993, 50:306–317.
45. Bulbena A, Duró JC, Porta M, et al.: Clinical assessment of hypermobility of joints: assembling criteria. J Rheumatol 1992, 19:115–122.
46. Grahame R: Brighton diagnosis criteria for the benign joint hypermobility syndrome. Br J Rheumatol 2000, 27:1777–1779.