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Somatic Conditions Intrinsic to Anxiety Disorders

Antonio Bulbena and Guillem Pailhez
Anxiety Disorders Unit – INAD, Barcelona
Spain

1. Introduction

Although Johann Christian August Heinroth (1773-1843) introduced the term 'psychosomatic' into medical literature, up to the present day his contributions to the development of medicine and psychosomatics have been little acknowledged. The relationship between somatic and psychiatric conditions is assumed to be fluent; however, the concept "psychosomatic" brings with it a heavy semantic burden that has its roots in the philosophical dualism, accentuated in the Cartesian proposal, which has spread through modern rationality, and, with it, the conception of the disease in the medical field.
The modern notion of health and illness make necessary to review dualistic positions, but often the everyday clinical practice still shows separated approaches for the mental and the somatic parts of the patient's illness. A clear example of this useless but very spread dualistic approach is the group of anxiety disorders, which have been included alternatively among the somatic and among the mental conditions when, in fact, anxiety disorders include both strong somatic and mental dimensions which need to be dealt with. In this chapter we shall review the link of the joint hypermobility syndrome (JHS) and several anxiety conditions. This relationship is probably one of the strongest available evidences of the somatic components of anxiety disorders.

2. Somatic conditions related with anxiety disorders

Anxiety disorders are related with other medical illness and have also been associated with high rates of medically unexplained symptoms and increased utilization of healthcare resources (McLauglin et al., 2006) and poor quality of life and disability (Sareen et al., 2006). Patients with anxiety disorders often complain of somatic features, especially cardiac (tachycardia, chest pain), gastrointestinal (epigastric pain), and neurological complaints (headaches, dizziness, or presyncope), in emergencies and primary services (Muller et al., 2005; Wells et al., 1989; Zaubler & Katon, 1998). This clinical phenomenon helped to deepen into the study of differential diagnoses between somatic symptoms of anxiety and somatic symptoms of comorbid conditions (Katon & Roy-Byrne, 1989; Stein, 1986; Wise & Taylor, 1990). More recent research suggests a strong association between anxiety disorders and somatic conditions, although some authors emphasize the huge amount of published research about somatic conditions and depression in contrast to the few studies about the same relationship with anxiety disorders (Harter et al., 2003; Roy Byrne et al., 2008;

Sareen et al., 2005). Furthermore, results from the National Comorbidity Survey-Replication (NCS-R) showed that various anxiety disorders had equal or greater association than depression with four chronic physical disorders (hypertension, arthritis, asthma, and ulcers) (Kessler et al., 2003).

The more recent review articles about this relationship are organized according to medical illness specifically associated to anxiety disorders in several descriptive and analytic studies with clinical samples (Katon, 1996; Muller et al., 2005; Roy Byrne et al., 2008; Simon & Fischmann, 2005; Wells et al., 1989). These reviews often include the following somatic conditions: irritable bowel syndrome, asthma, cardiovascular disease, cancer, chronic pain, vestibular and thyroid dysfunction, chronic obstructive pulmonary disease, and mitral valve prolapse. Some of the main general conclusions of these reviews are the following: 1) emerging evidence about the bi-directional relationship between anxiety disorders and medical illness suggests that they may be as important as depression (Roy Byrne et al., 2008); 2) such associations provide important clues for understanding the neurobiology of anxiety disorders (Muller et al., 2005); and 3) such associations are greater for panic disorder (Katon, 1996; Wells et al., 1989), worsening its identification, presentation and treatment (Simon & Fischmann, 2005).

Along this way, there are four studies relying on clinical samples that have shown higher rates of somatic conditions among patients with anxiety disorders. The first one was published in 1994. Rogers et al. examined the prevalence and characteristics of medical illness in 711 patients with present or past index anxiety disorders (Rogers et al., 1994). Patients were assessed using structured diagnostic interviews and the Medical History Form II. The rates of medical illness for all subjects were later compared with data extracted from an epidemiological sample. Results showed that patients with panic disorder had more reported medical problems than the general population, in particular, more ulcer disease, angina, and thyroid disease.

In 2003, Härter et al. studied the associations between anxiety disorders and medical illnesses in a total of 262 probands (169 cases with an anxiety disorder and 93 controls with no evidence of an anxiety disorder according to DSM-III-R criteria) (Härter et al., 2003). Diagnoses were obtained based on direct interview (SADS) or family history information, and lifetime history of numerous medical illnesses was obtained. Results showed that patients with a lifetime anxiety disorder reported higher rates of several medical illnesses than did persons without anxiety. After controlling for the effects of gender, comorbid substance abuse/dependence and/or depression, significant associations were found between anxiety disorders and cardiac disorders (OR = 4.6), hypertension (OR = 2.4), gastrointestinal problems (OR = 2.4), genitourinary disorders (OR = 3.5), and migraine (OR = 5.0). A similar pattern was observed for probands with panic or generalized anxiety disorder.

Sareen et al. examined the relationship between anxiety disorders and a wide range of physical conditions in a nationally representative sample. Data came from the National Comorbidity Survey (N=5,877). Physical disorders were assessed based on a list of several conditions shown to respondents. Results showed that anxiety disorders were positively associated with physical conditions even after adjusting for mood disorders, substance-use disorders, and sociodemographics. Among specific anxiety disorders, panic disorder and agoraphobia were more likely to be associated with cardiovascular disease and bone and joint diseases (Sareen et al., 2005).

In 2008, in a case-control study carried out by our group (Pascual et al., 2008) using retrospective data extracted from clinical records, patients with anxiety disorders showed

higher risk of medical illnesses than patients without anxiety disorders. The aim of the study was to investigate the comorbidity between anxiety disorders and somatic conditions in three groups: patients with anxiety disorders (n=130) including panic disorder with/without agoraphobia and agoraphobia without panic attacks, patients from a primary care unit without any psychiatric disorder (n=150), and patients from a psychiatric service without anxiety disorders (n=130). Multivariate statistical logistic regression analysis showed that patients with anxiety disorders presented 4.2-fold increase in the risk of cephalea, 3.9 of cardiopathy, 3.8 of osteomuscular disorder and 2-fold increase in the risk of digestive diseases.

There are various hypotheses on how anxiety disorders and medical conditions may be related (Rogers et al., 1994). Medical illness may sometimes directly trigger the development of anxiety symptoms (e.g., cardiomyopathy or anxiety as a psychological reaction towards an illness), or mimic anxiety symptoms (e.g. pheochromocytoma). Conversely, anxiety disorders may sometimes directly trigger the development of somatic symptoms (e.g., angina in cardiovascular disease), mimic symptoms of a medical illness (leading to high costly procedures or inadequate treatment), or may contribute to the onset or exacerbation of certain somatic conditions (e.g., hypertension or gastric ulcer).

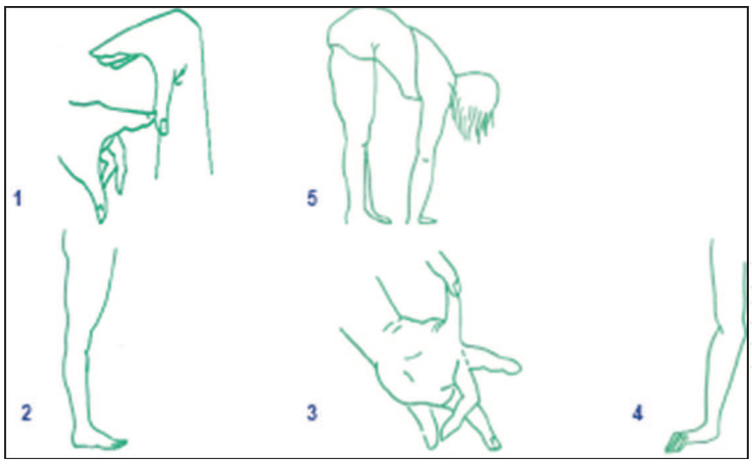
However, there is evidence that some medical conditions that are often comorbid with anxiety disorders could share a common genetic etiology (Collier, 2002; Gratacos et al., 2001; Pailhez et al., 2009). For example, a recent family study found that panic or social anxiety patients and their first-degree relatives were more likely to have interstitial cystitis, mitral valve prolapse and headaches, and this was hypothesized to be linked to a common genetic susceptibility. Talati et al. studied probands with diagnosis and family history of panic disorder (n=219), social anxiety disorder (n=199), or both (n=173), and 102 control subjects with no personal/family history of anxiety. Subjects were blindly interviewed with a diagnostic instrument and medical history was obtained via medical checklist and the family history screen (Talati et al., 2001).

3. Anxiety disorders and the role of collagen tissue

According to this hypothesis, several studies have shown a noticeable association between anxiety disorders (particularly panic/phobic cluster) and the joint hypermobility syndrome (JHS) (Bulbena et al., 1993; Bulbena et al., 2004; Bulbena et al. 2007). JHS is an inherited connective tissue disorder associated with a generalized collagen laxity and characterized by an increase of active or passive joint mobility. The condition was not described for the first time until fifty years ago, when it was properly identified and associated to pathology of the musculoskeletal system (Rotés & Argany, 1957). In 1973, after an epidemiological study by Beighton et al., the syndrome gained general interest in the rheumatological field and began to be studied in a broader way, as a separate entity (Beighton et al., 1973) (see Fig.1).

In 1992, the Hospital del Mar criteria (table 1) compiled all the items included in the most clinically used criteria. This new scale showed consistent indicators of reliability, internal consistency and predictive validity, and provided evidence for using different scores according to age and gender (Bulbena et al., 1992).

JHS has an estimated prevalence in the general population ranging between 10% – 15%, it is more frequent among females (3:1) and is one of the hereditary disorders of the connective tissue, which include other conditions such as Ehlers-Danlos syndrome, Marfan syndrome and ostogenesis imperfecta (Beighton et al., 1999). Clinical features in JHS can be articular or



1. Passive apposition of the thumbs to the flexor aspects of the forearm (one point for each thumb).
2. Hyperextension of the knee beyond 10º (one point for each knee).
3. Passive dorsiflexion of the little fingers beyond 90º (one point for each hand).
4. Hyperextension of the elbows beyond 10º (one point for each elbow).
5. Forward flexion of the trunk with knees fully extended so that the palms of the hands rest flat on the floor (one point).

Fig. 1. Joint Hypermobility criteria (Beighton et al., 1973)

Upper extremities
1. Passive apposition of the thumb to the flexor aspect of the forearm at a distance of less than 21 mm.
2. The passive dorsiflexion of the fifth finger is 90º or more.
3. The active hyperextension of the elbow is 10º or more.
4. External rotation of the shoulder up to more than 85º.
Lower extremities. Supine position
5. The passive hip abduction can be taken to an angle of 85º or more.
6. Hypermobility of the rotula.
7. Hypermobility of the ankle and foot.
8. Dorsal flexion of the toe of 90º or more.
Lower extremities. Prone position
9. Hyperflexion of the knee.
10. Ecchymoses.

Table 1. Hospital del Mar criteria (Bulbena et al., 1992) for JHS. Male patients scoring 4 or more are considered cases; female patients are considered cases with scores 5 or over.

extra-articular and are always related to the connective tissue. Among the best known articular features of JHS are arthralgia, lumbalgia, soft-tissue rheumatism (e.g., epicondilytis, tenosynovitis, bursitis), recurrent dislocations, childhood scoliosis, or rheumatoid arthritis (Bravo, 2009; Keer & Grahame, 2003). Among the best-known extra-articular features of JHS are hernias, varicose veins, "easy bruising", keloids, uterine or rectal prolapse, spontaneous pneumothorax, fibromyalgia, dysautonomia and some other conditions also linked to panic disorder as asthma, mitral valve prolapse, thyroid dysfunction or irritable bowel syndrome (Keer & Grahame, 2003; Mishra et al., 1996). Therefore, most of the conditions linked to anxiety

disorders can be explained as clinical features of JHS. Unfortunately, the relationship between anxiety disorders and JHS is often neglected.

The clinical relationship between anxiety disorders and JHS was found 50 years ago. In 1957, the rheumatologist J. Rotés Querol pointed out for the first time the remarkable degree of nervous tension suffered by patients with hypermobility (Rotés & Argany 1957). To a certain extent, there are some indirect references about the relationship between "hypotonia" and anxiety/phobias in the classical psychosomatic literature (Flanders, 1950). On the other hand, Carlsson and Rundgren in 1980 (Carlsson & Rundgren 1980) found a higher score in hypermobility among alcoholic patients than among controls. Although not mentioned, the percentage of anxiety patients among the case group might have been high.

Empirical history of the clinical relationship between anxiety disorders and JHS starts in the case-control study conducted by our group in 1993, with rheumatologic outpatients affected by JHS (Bulbena et al., 1993). Diagnoses of panic disorder, agoraphobia and simple phobia were significantly more frequent among hypermobile patients. There were no significant differences in the diagnoses of generalized anxiety disorder, dysthymia, or major depressive disorder. Around 70% of rheumatological patients with JHS had some kind of anxiety disorder. However, this only occurred in 22% of controls, a usual figure in chronic patient samples. Cases were 10 times more likely to suffer from anxiety than controls. Specifically, agoraphobia and panic disorders were, respectively, 5 and 7 times more likely (table 2).

	% JHS	% Non-JHS	Age-Sex Adjust. Odds Ratio	95 % C. I.
Any Anxiety D.	69,3	22,0	**10.69**	4.80-23.81
Panic D.	34.2	6.8	**6.96**	2.31-20.91
Panic & Agora.	24.6	5.1	**6.40**	1.82-22.43
Simple Phobia	29.8	8.5	**5.77**	2.05-16.24
Agoraphobia	37.7	11.9	**5.08**	2.06-12.49
General.Anx.	10.5	5.1	**2.49**	0.65-9.45
Major Depress.	14.9	3.4	**4.51**	0.99-20.56
Dysthymic D.	7.9	5.1	**2.15**	0.53-8.65

Table 2. Lifetime psychiatric disorders in JHS cases (n=114) and non-JHS controls (n=59) seen at an outpatient rheumatological unit (Bulbena et al., 1993).

For a subsequent second study, conducted to support this hypermobility-anxiety association, outpatients with new diagnoses of panic disorder and/or agoraphobia were examined, as well as non-anxious psychiatric and non-psychiatric outpatients as control groups (Martín-Santos et al., 1998). Results showed that JHS was present in almost 70% of anxiety cases, versus slightly over 10% of controls. This meant that cases with panic disorders and/or agoraphobia were 17 times more likely to suffer from JHS. Conclusions were valid particularly for women, but also for men (figure 2).

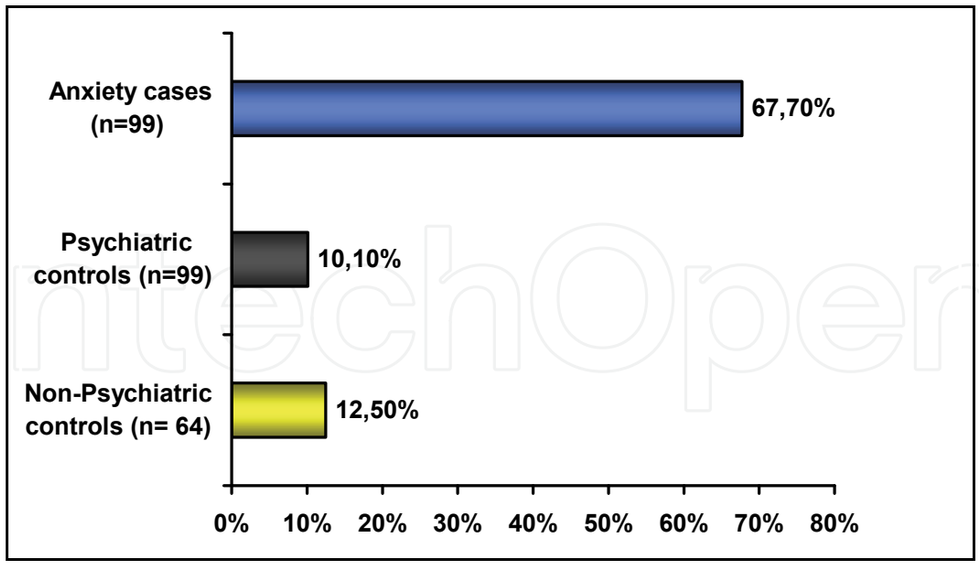


Fig. 2. Frequency of JHS diagnoses in anxiety cases (n=99), psychiatric (n=99) and non-psychiatric controls (n=64) (Martín-Santos et al., 1998). [O.R. = 16.9; CI 95% 8.8 to 32.2].

Later on, it was suggested that this association needed to be studied in the general population. To that end, a two-phase cross-sectional epidemiological study was carried out in a rural town in order to establish lifetime risk for anxiety and affective disorders in subjects with JHS. A sample of 1,300 individuals were examined at baseline and over 500 were subsequently subjected to follow-up in a two-stage epidemiological study. Hypermobile patients were eight times more likely to suffer from panic disorder (OR 8.2, CI 95% 3.4 to 19.7), eight times more likely to suffer from social phobia (OR 7.8; CI 95% 2.4 to 24.8) and six times more likely to suffer from agoraphobia (OR 5.9; CI 95% 3 to 11.7) than non-JHS patients. Results were valid for both genders. No differences were found for other anxiety disorders or mood disorders (Bulbena et al., 2004a).

In the same sample of general population it was also reported that hypermobiles had significantly higher scores in fear and phobia scales, reinforcing the hypothesis that intensity of fears is greater in subjects with JHS (Bulbena et al., 2006). We assessed fear intensity and frequency using a modified version of the Fear Survey Schedule (FSS-III). When we compared the groups with and without joint hypermobility, the mean total scores for both genders were significantly higher for the hypermobile group (figure 3). These results showed that the association of JHS and phobic anxiety is sustained for intense fears and might represent a susceptibility factor for these anxiety conditions.

In 2005, we studied schizophrenic outpatients (N=124) with the hypothesis that anxiety disorders mediated by JHS were not symptoms, but an independent comorbid entity in schizophrenic patients (Bulbena et al., 2005; Bulbena et al., 2007). Joint Hypermobility was noticeably more likely among panic disorder/phobia-clustered schizophrenic patients, than among the non-comorbid group (OR = 9.35; IC = 95% [3.85-22.73]; $p<0.0001$). The cluster panic disorder/phobia had higher scores in fear scales and schizophrenia positive symptom scales.

After several significant cross-sectional studies we sought to conduct a prospective incidence analysis that assesses whether JHS could be a risk factor in developing anxiety conditions (Bulbena et al., 2011).

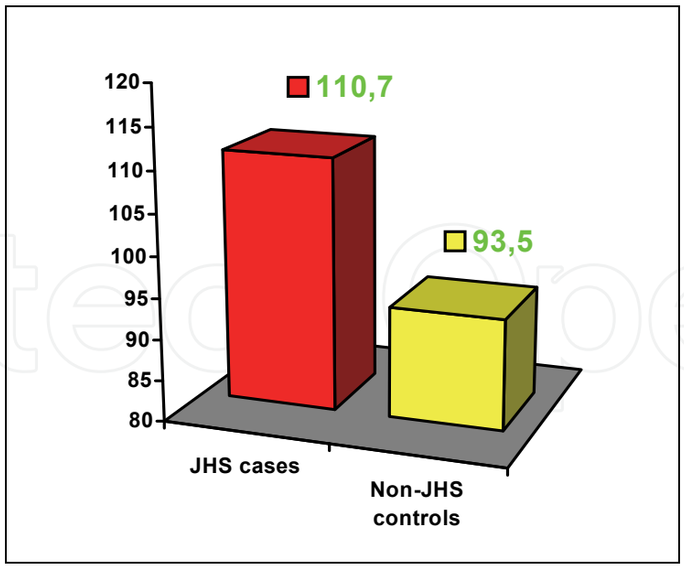


Fig. 3. Mean total scores of the Fear Survey Schedule (FSS-III) in JHS cases (n=182) and non-JHS controls (n=1,123) (Bulbena et al., 2006).

In 2004, our group also assessed a non-clinical sample of subjects working in the same company (N=526) (Bulbena et al., 2004b). Subjects with JHS had significantly higher scores in STAI trait anxiety [female average: 16.5 vs. 11, $p<0.001$] [male average: 13 vs. 11, $p<0.03$]. STAI state anxiety scores were also higher among hypermobile subjects, although not significantly (figure 4).

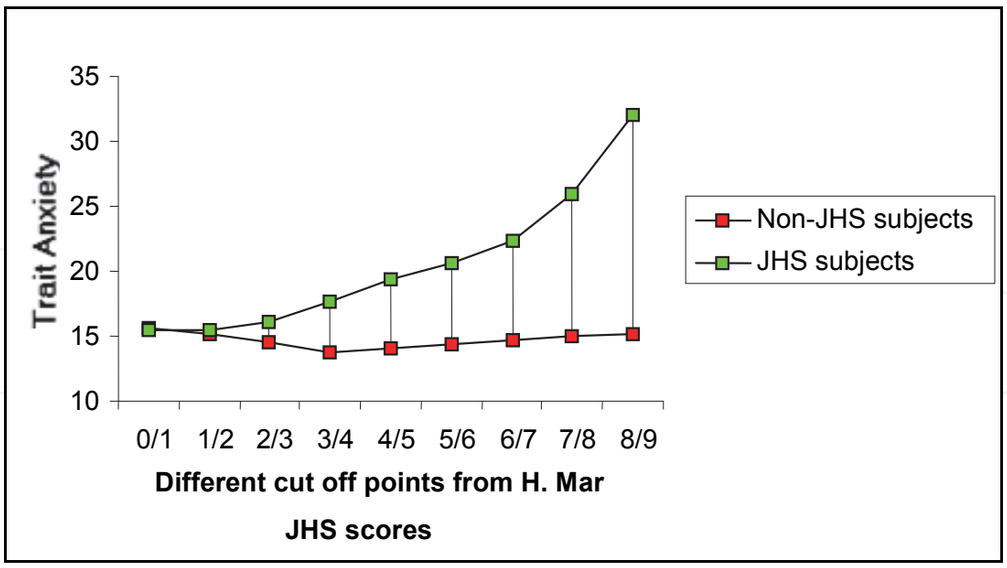


Fig. 4. Trait anxiety in 203 women with or without joint hypermobility according to all possible cutoff scores on the Hospital del Mar hypermobility criteria (Bulbena et al., 2004b).

The main objective was to determine the cumulative incidence of anxiety disorders in a cohort of young subjects recruited from the general population who had not developed any type of anxiety condition up to then; consequently we planned a scheduled 15-year follow-

up covering subjects from late adolescence to adulthood. The total population sample was 1,305 subjects, and in order to observe the development of anxiety disorders during the 15-year study period, only the lower age segment (at that time subjects aged between 16 and 20) included in the town's municipal registry was invited to participate. We sought to describe the occurrence of new cases of anxiety disorders during the study period, therefore the exclusion criterion for the study was having already had an anxiety disorder at baseline examination. At baseline, 158 subjects were screened for participation in the study, and after the 15-year follow-up the final sample comprised 137 subjects (86.7% retention rate). Results showed that cumulative incidence of panic/agoraphobia at follow-up was significantly higher for the JHS group (41.4%) than for the control group (1.9%) with relative risk of 22.3 (CI 95% 4.6-108.7), p<0.0001, (NNT 3, CI 95% 2.9-2.3). Incidence of social phobia and simple phobia was also significantly higher for the JHS group at (RR=6.52; CI 95% 1.7-24.2) p<0.001 and (RR=3.31; CI 95% 1.1-9.6) p=0.02, respectively. Moreover, anxiolytic drug use was nearly fourfold higher among JHS subjects compared to non-JHS.

Total Sample n = 137	**JHS Status**						
	JHS present *n* = 29		JHS absent *n* = 108				
	n	%	*n*	%	*RR*	95% CI	*P*
Anxiety Disorders							
Panic/Agoraphobia	12	41.4	2	1.9	22.3	(4.6 to 108.7)	0.0001***
Social Phobia	7	24.1	4	3.7	6.5	(1.7 to 24.2)	0.001*
Simple Phobia	8	27.6	9	8.3	3.3	(1.1 to 9.6)	0.02*
GAD	7	24.1	9	8.3	2.9	(0.97 to 8.62)	0.14 ns
Other Disorders							
Depression/Dysthymia	7	24.1	7	6.48	3.7	(1.2 to 11.7)	0.15 ns
JHS, Joint Hypermobility Syndrome according to Beighton criteria assessed at baseline. GAD, Generalized Anxiety Disorder Statistical significance: * p<0.05, ** p<0.001, *** p<0.0001, ns: non significant.							

Table 3. Incident cases and relative risk after 15 years of follow-up according to JHS status (Bulbena et al., 2011).

Recent work from another Spanish group, (García-Campayo et al., 2010) has shown again a high prevalence of JHS (61.8%) among panic subjects compared with 10.9% in the healthy control group and 9% in the psychiatric control group. Interestingly these authors found an intermediate figure among subjects suffering from fibromyalgia (25.4%). A paper from a Turkish group, albeit declaring no significant association, also found JHS in 59.5% of panic disorder patients with mitral valve prolapse, in 42.9% of patients without mitral valve prolapse but also in 52.6% of control subjects (Gulpek et al., 2004). Gülsün et al., studying subjects with thorax deformities, found that the anxiety level of males with thorax deformity and JHS is higher than males with thorax deformity without JHS (Gülsün et al., 2007). And finally, Baeza-Velasco and Bulbena also found high prevalence of social anxiety and joint hypermobility among subjects of high stature (Baeza-Velasco & Bulbena 2009).

	Type	Popul.	N groups	Sex	Age	JHS ass.	Association tendencies
Bulbena et al., 1993	CC	Spain	114 JHS 59 CTL	Matched	Matched	Beighton	JHS cases: 5 x Aph and 7 x PD
Martin-Santos et al., 1998	CC	Spain	99 PD & APh 99 Psychiatric CTL 64 Medical CTL	Matched	Matched	Beighton	PD cases: 17 x JHS
Benjamin et al., 2001	CC	Israel	101 PD 39 Healthy CTL	35 / 65 64 / 36	39.3 (11) 23.4 (3)	Beighton	No statistically significant relationship
Bulbena et al., 2004a	E	Spain	1305 subjects	45.7 / 54.3	43.4 (18.3)	Beighton	JHS cases: 6 x Aph, 8 x SPh and 8 x PD
Gulpek et al., 2004	CC	Turkey	42 PD & MVP 35 PD 38 MVP CTL	Matched	Matched	Beighton	No statistically significant relationship
Bulbena et al., 2004b	D	Spain	526 subjects	61.4 / 38.6	25.4 (3)	H. Mar	JHS cases: higher scores in STAI trait anxiety
Bulbena et al., 2005 & 2007	D	Spain	124 SCHZ	54 / 46	33.6 (10)	Beighton & H. Mar	Schizophrenic & PD cases: 9 x JHS and higher positive symptoms
Bulbena et al., 2006	D	Spain	1305 subjects	45.7 / 54.3	43.4 (18.3)	Beighton	JHS cases: higher scores in fear and phobia scales
Gülsün et al., 2007	CC	Turkey	52 thorax deformity 40 CTL	Males	21.9 (1.3)	Beighton	JHS cases: higher scores in HAM-A
Baeza-Velasco & Bulbena 2009	D	Several countries	158 high stature	46.8 / 53.2	25.7 (8.1)	Hakim & Grahame	JHS cases: higher scores in LSAS
García-Campayo et al., 2010	CC	Spain	55 PD 55 Psychiatric CTL 55 Fibromyalgia 55 Healthy CTL	Matched	Matched	Beighton	PD cases: 13 x JHS
Bulbena et al., 2011	C	Spain	137 subjects	53.3 / 46.7	31.9 (2.4)	Beighton & H. Mar	JHS cases: 22 x PD, 6.5 x SPh and 3.3 x Ph

Table 4. Relationship between JHS and anxiety disorders. Basic features of studies reviewed. D, descriptive study; CC, case–control study; C, cohort study; E, epidemiological study; CTL, controls; PD, Panic disorder; Aph, Agoraphobia; MVP, Mitral valve prolapse; SCHZ, Schizophrenia; SPh, Social phobia; Ph, Specific phobia. Sex expressed in percentage (%) male/female. Age expressed in mean (SD).

4. Perspectives

There is enough evidence showing that comorbidity of anxiety disorders and some medical conditions share a similar physiopathological mechanism mediated by the clinical features of JHS. Having arrived at this point, it might be relevant to remind the high association of JHS and the so called dysautonomia. In this way, significant research by Gazit and colleagues (Gazit et al., 2003) found that symptoms related to anxiety such as palpitations, light-headedness, nausea, shortness of breath, hyperventilation, tremulousness, chest discomfort, fatigue, etc., were significantly more common among patients with JHS. Moreover, they found that orthostatic hypotension, postural orthostatic tachycardia syndrome and uncategorized orthostatic intolerance were present in 78% of the studied patients with JHS compared to 10% of control subjects. Thus, they suggested that dysautonomia could be an extra-articular related feature of JHS.

However, under the "modern" name dysautonomia not only anxiety features can be found (Bulbena et al, 2004c) but also many symptoms described for more than two centuries in the present group of anxiety disorders (Berrios, 1999). Anxiety manifestations are among the most difficult to identify in the clinical practice even in patients suffering from generalized anxiety disorder, in which only 13% present anxiety as main complaint. Although dysautonomia and anxiety disorders are not in the same spectrum, they probably overlap. Therefore, the link between JHS and dysautonomia provide an interesting physiological connection to interpret this unexpected association between a "somatic" and a "psychiatric" condition.

Our results address the biological basis of anxiety and a common source of this condition with other constitutional disturbances in relation to connective tissue and the autonomic nervous system. Patients with a diagnosis of JHS provide a highly valuable opportunity for an in-depth study of the genetic basis of anxiety. Anxiety is also a comorbidity and a risk factor in itself for a poor prognosis in several psychiatric diseases, as is the case with schizophrenia and bipolar disorders. These diseases also provide opportunities to further explore the connection between joint hypermobility and the development of anxiety in these conditions.

It is also important to point out a possible application of this evidence; as patients with JHS are at greater risk of suffering from anxiety conditions, it would be desirable to prevent the development of anxiety disorders by means of community programs at the very early stages of development. We strongly recommend screening for joint hypermobility in routine health assessment protocols in teenagers and early adulthood subjects. Even though the clinical evaluation of JHS is not extremely difficult, it does inevitably require formal training and an external validation of the procedure. In this context, some anamnestic questions might be useful for detecting positive cases at risk of suffering from anxiety disorders.

5. Conclusions

Finally, several conclusions can be made after more than 30 years of active research and clinical work in that field.

First, the association between anxiety (clinical and non clinical) and JHS is strong and replicated in several setting and samples.

Second, both conditions carry high genetic and heritable load. This is clinically very well established, but at the genetic level, there is no clear conclusion yet. Our finding of both conditions in the chromosome 15 is now actively revisited.

Third, according to the type and number of somatic conditions found in the otherwise named "endogenous" anxiety disorders (panic, agoraphobia and social phobia), it seems that these patients tend to suffer from a particular cluster of disorders, particularly, osteo-muscular, irritable bowel, hypo/hyperthyroid, migraine, asthma, etc. It might well be that all these conditions share some common abnormalities in the autonomic nervous system as well as in the collagen structure as found in JHS. This may be a diathesis not yet identified, but worthy to investigate.

And fourth, the autonomic disregulation, although very difficult to assess at that level, may be one of the clues to understand the association, and also to develop appropriate treatments.

In summary, this intriguing relationship gives rise to several physio-pathological questions and prevention-related issues. JHS is a risk factor for anxiety disorders, worthy of evidence-based identification in the context of preventive psychiatry not only among adults but also among at-risk pediatric populations.

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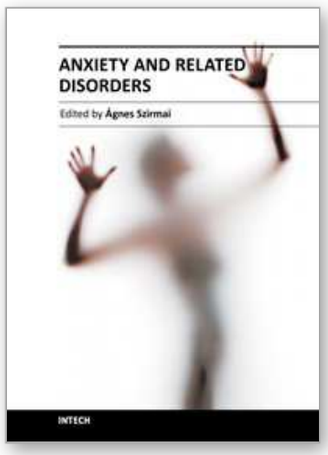

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Anxiety disorders are one of the most common psychiatric disorders worldwide and many aspects of anxiety can be observed. Anxious patients often consult primary care physicians for their treatment, but in most cases they do not accept the diagnosis of anxiety disorder. Anxiety is a symptom that could be seen in many organic disorders and can accompany almost any psychiatric disorder. Anxiety disorders are frequent and are associated with significant distress and dysfunction. Stigmatization is an important factor in insufficient diagnosis. The problems of anxiety cover all fields of life. This book intends to describe the epidemiological aspects and the main co-morbidities and consecutive diseases of the anxiety disorders.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
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Phone: +385 (51) 770 447
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