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Chapter 9

Co-Morbid Anxiety and Physical Disorders: A Possible Common Link with Joint Hypermobility Syndrome

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Additional information is available at the end of the chapter

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1. Introduction

As we stated in a previous book chapter titled "Somatic conditions intrinsic to anxiety disorders" [1], Johann Christian August Heinroth (1773-1843) was the person who introduced for the first time the term 'psychosomatic' into medical literature. The psychosomatic approach offers an overall or holistic "body and mind" perception that can be often useful for prevention purposes. Unfortunately, up to the present day Heinroth's contributions to the development of medicine and psychosomatics have been little acknowledged. Possibly, the current medical tendency towards specialisation makes it difficult to embody such paradigms in current psychiatric and medical nosology.

In this sense, the group of anxiety disorders 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. The study of somatic conditions linked to anxiety disorders provide insights into the biology of these mental disorders that may result in a greater understanding of its aetiology, treatment, and prevention. In this second chapter we shall review, up to the last findings, the comorbidity of anxiety and physical disorders linked to joint hypermobility syndrome (JHS). This relationship is one of the strongest available evidences of the somatic components of anxiety disorders.

2. Anxiety disorders do relate to some somatic conditions

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 [2-4]. This clinical

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phenomenon helped to deepen into the study of differential diagnoses: are they symptoms of the primary anxiety disorder or are they symptoms of a comorbid physical illness? [5-7]. Besides, 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 [8-10]. 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) [11].

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 [2,3,9,12,13]. 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 [9]; 2) such associations provide important clues for understanding the neurobiology of anxiety disorders [2]; and 3) such associations are greater for panic disorder [12,3], worsening its identification, presentation and treatment [13].

Along this way, there are four studies relying on clinical samples that have shown higher rates of somatic conditions among patients with anxiety disorders (table 1). 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 [14]. 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) [8]. 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.

In 2005, 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

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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 [10].

In 2008, in a case-control study carried out by our group [15] 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.

	Type	N	Data assessment	Main associations
Rogers et al. 1994 [14]	D	711	Structured diagnostic interview	Ulcer disease, angina & thyroid disease
Härter et al. 2003 [8]	CC	262	Direct interview & medical records	Cardiac disorders, hypertension, digestive problems, genitourinary disorders & migraine
Sareen et al. 2005 [10]	E	5877	List of several conditions	Cardiac disorders & bone and joint diseases
Pascual et al. 2008 [15]	CC	410	Medical records	Cephalea, cardiac disorders, bone and joint diseases & digestive problems

Table 1. Relationship between medical conditions and anxiety disorders. Basic features of studies reviewed. D, descriptive study; CC, case–control study; E, epidemiological study.

3. Measuring medical conditions in anxiety patients

Despite the significant prognostic and therapeutic implications derived from the comorbidity between mental disorders and medical conditions, there is a lack of measuring instru-

ments designed to quantify the physical health and disease in psychiatric population. Obviously, the use of these instruments in clinical settings is virtually absent. In this sense, our team developed, for over a decade, the Spanish version of the Cumulative Illness Rating Scale [16] designed for the assessment of medical conditions in general. The issues chosen for this instrument to assess illness severity were related to life-risk, functional disability and the need for treatment. Our group is now actively working on a variation of this scale, specially designed to detect medical conditions, including some functional diseases, on anxiety and depressive patients. Some of these functional diseases assessed are atopy and allergies, tensional headache and migraine, fibromyalgia, irritable bowel syndrome, dysfagia and dyspepsia, interstitial cystitis, sexual dysfunction, temporo-mandibular joint disorder, and chronic fatigue syndrome.

There are various hypotheses on how anxiety disorders and medical conditions may be related [14]. 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 [17-19]. For example, 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 [20]. They 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. According to this hypothesis, several studies have shown a noticeable association between anxiety disorders (particularly panic/phobic cluster) and the joint hypermobility syndrome (JHS) [21-23]. This association has allowed a wider "body and mind" comprehension of anxiety disorders and has provided new clues in order to measure medical conditions in these patients.

4. Anxiety disorders and the role of collagen tissue

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 by Rotés, when it was properly identified and associated to pathology of the musculoskeletal system [24]. 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 [25] (see Fig.1).

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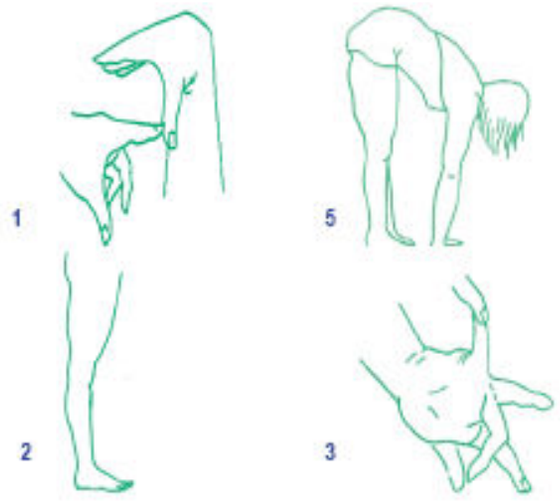


Figure 1. Joint Hypermobility criteria [25]1.Passive apposition of the thumbs to the flexor aspects of the forearm (one point for each thumb). 2. Hyperextension of the knee beyond 10º (one point for each knee). 3. Passive dorsiflexion of the little fingers beyond 90º (one point for each hand). 4. Hyperextension 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).

In 1992, the Hospital del Mar criteria (table 2) 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 [26].

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

Table 2. Hospital del Mar criteria for JHS [26]. Male patients scoring 4 or more are considered cases; female patients are considered cases with scores 5 or over.

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 ostogenesisimperfecta [27]. Clinical features in JHS can be articular or 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 [28,29]. 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 [29,30]. 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. RotésQuerol pointed out for the first time the remarkable degree of nervous tension suffered by patients with hypermobility [24]. To a certain extent, there are some indirect references about the relationship between "hypotonia" and anxiety/phobias in the classical psychosomatic literature [31]. On the other hand, Carlsson and Rundgren in 1980 [32] 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 [21]. 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 3).

	% 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 3. Lifetime psychiatric disorders in JHS cases (n=114) and non-JHS controls (n=59) seen at an outpatient rheumatological unit [21].

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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 [33]. 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 for women [OR=23.7; CI95% 10.6-52.9] (figure 2), but also for men [OR=10.5; CI95% 3.0-36.3] (figure 3).

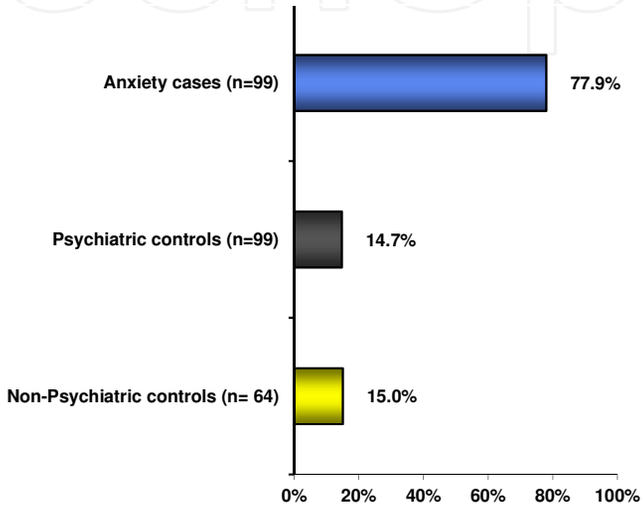


Figure 2. Women frequencies of JHS diagnoses in anxiety cases (n=99), psychiatric (n=99) and non-psychiatric controls (n=64) [33].

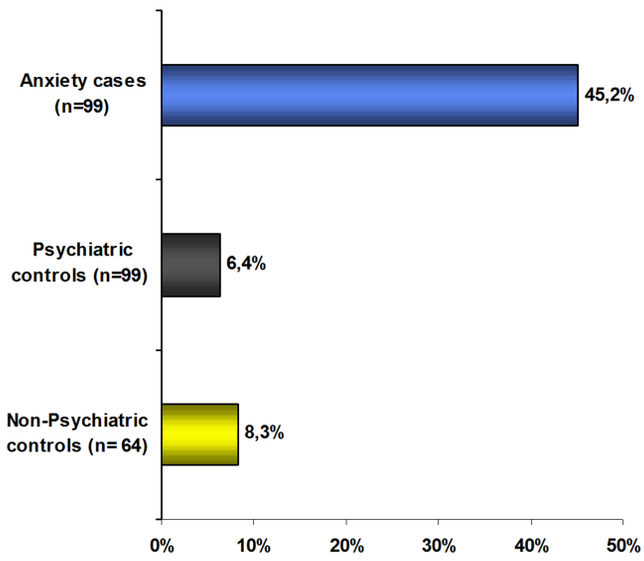


Figure 3. Men frequencies of JHS diagnoses in anxiety cases (n=99), psychiatric (n=99) and non-psychiatric controls (n=64) [33].

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 [22].

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 [34]. 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 4). 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.

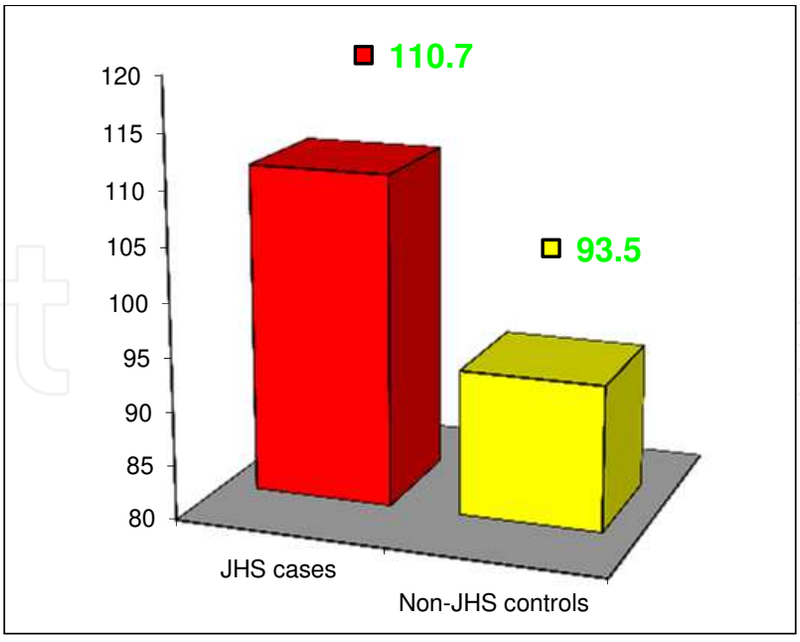


Figure 4. Mean total scores of the Fear Survey Schedule (FSS-III) in JHS cases (n=182) and non-JHS controls (n=1,123) [34].

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The same design was replicated in 2011 in a sample of 150 nonclinical students [35]. Severe fears and daily consumption of cigarettes, alcohol, coffee, and chocolate were compared with the hypermobility scores. We found significant differences when comparing severe fears between the groups with and without hypermobility (7.6 vs. 11; p = 0.001). The frequency of chocolate intake was also significantly higher among subjects with joint hypermobility (31.2% vs. 51.2%; p = 0.038). There were no significant differences regarding cigarette (19.5% vs. 19.3%), alcohol (36.6% vs. 34.9%), and coffee (46.3% vs. 35.8%) consumption. Therefore, these patterns of consumption may be interpreted as self-treatment attempts of subsyndromal anxiety in hypermobile subjects (figure 5).

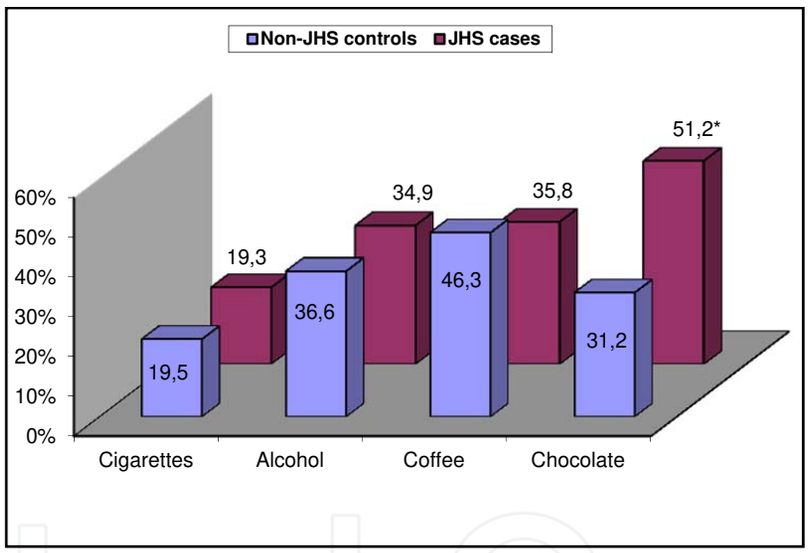


Figure 5. Frequencies of daily consumption of cigarettes, alcohol, coffee, and chocolate in JHS cases (n=41) and non-JHS controls (n=109) [35]. *p = 0.038

In 2004, our group also assessed a non-clinical sample of subjects working in the same company (N=526) [36]. 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 6).

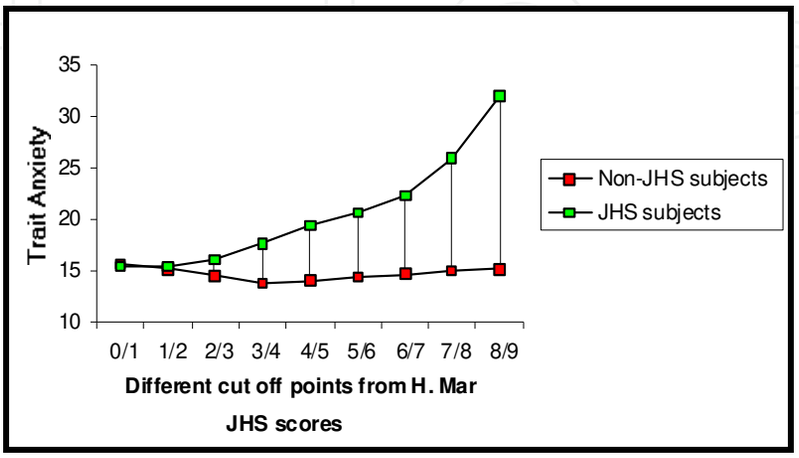


Figure 6. STAI trait anxiety scores (range: 0-60) in 203 women with or without joint hypermobility according to all possible cutoff scores on the Hospital del Mar hypermobility criteria [36].

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 [37,38]. 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. We are now performing a voxel-based morphometric study in order to examine brain structure, comparing magnetic resonance images of 20 schizophrenic-anxious patients and 20 schizophrenic patients. The preliminary results indicated gray matter volume differences in the schizophrenic-anxiety group in the dorsolateral prefrontal cortex related to the interaction between both conditions. Our findings suggest that the schizophrenic-anxiety group is characterised by specific neural abnormalities that cannot be explained by the presence of schizophrenia or anxiety, but by their conjunction, and this might result in a certain symptomatology [39].

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 [23].

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-

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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 (table 4). Moreover, anxiolytic drug use was nearly fourfold higher among JHS subjects compared to non-JHS.

Recent work from another Spanish group [40] 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 [41], 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. Gülsün et al. [42], 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. And finally, Baeza-Velasco [43] also found high prevalence of social anxiety and joint hypermobility among subjects of high stature.

Total Sample n = 137	**JHS Status**				*RR*	*95% CI*	*P*
	JHS present *n* = 29		JHS absent *n* = 108				
	n	%	*n*	%			
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 4. Incident cases and relative risk after 15 years of follow-up according to JHS status [23].

	Type	Popul.	N groups	Sex	Age	JHS ass.	Association tendencies
Bulbena et al., 1993 [21]	CC	Spain	114 JHS 59 CTL	Matched	Matched	Beighton	JHS cases: 5 x Aph and 7 x PD
Martin-Santos et al., 1998 [33]	CC	Spain	99 PD &APh 99 Psychiatric CTL 64 Medical CTL	Matched	Matched	Beighton	PD cases: 17 x JHS
Benjamin et al., 2001 [52]	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., 2004 [22]	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 [41]	CC	Turkey	42 PD & MVP 35 PD 38 MVP CTL	Matched	Matched	Beighton	No statistically significant relationship
Bulbena et al., 2004 [36]	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 [37,38]	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 [34]	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 [42]	CC	Turkey	52 thorax deformity 40 CTL	Males	21.9 (1.3)	Beighton	JHS cases: higher scores in HAM-A
Baeza-Velasco &Bulbena 2009 [43]	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 [40]	CC	Spain	55 PD 55 Psychiatric CTL 55 Fibromyalgia 55 Healthy CTL	Matched	Matched	Beighton	PD cases: 13 x JHS
Pailhez et al., 2011 [35]	D	Spain	150 subjects	44 / 56	16.4 (0.6)	Hakim & Grahame	JHS cases: higher scores in fear and phobia scales
Bulbena et al., 2011 [23]	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 5. 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).

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5. Weather, medical conditions and panic attacks

The relationship between meteorological variables and human behaviour has been subject of conjecture since Hippocrates. This interaction has been held more in popular belief than in scientific verification. However, since mid 1900s it has been more thoroughly studied, and we are now in a better position to test popular beliefs regarding this connection. Numerous studies in different fields have been carried out in an attempt to assess this relationship and its implications. Studies about meteorological variables and stroke onset [44], myocardial infarction [45] and arthritic pain [46] have shown significant results. Moreover, subjective experience from patients, such as variations in pain thresholds and mood swings when the weather changes, points towards this association and paves the road towards further research.

There are few studies designed to specifically assess the association between meteorological variables and clearly defined psychiatric disorders. Our group has studied this relationship with anxiety disorders [47]. Anxiety disorders are a clinically heterogeneous group that should be evaluated by differentiating panic and non-panic anxiety states due to the different clinical features present in each. Panic disorder has been associated with JHS, which is not seen in generalized anxiety disorder. Due to this association, the physical variables tend to be more relevant. This evidence has partly motivated the need to assess the association of meteorological variables with anxiety disorders and panic attacks separately and specifically.

All psychiatric emergencies attended at a general hospital in Barcelona (Spain) during 2002 with anxiety as main complaint were classified as panic or non-panic anxiety according to strict independent and retrospective criteria. Both groups were assessed and compared with meteorological data (wind speed and direction, daily rainfall, temperature, humidity and solar radiation). Seasons and weekend days were also included as independent variables. Episodes of panic were three times more common with the *poniente* wind (hot wind), twice less often with rainfall, and one and a half times more common in autumn than in other seasons (table 6). These three trends (hot wind, rainfall, and autumn) were accumulative for panic episodes in a logistic regression formula. Significant reduction of episodes on weekends was found only for non-panic episodes. Panic attacks, unlike other anxiety episodes, in a psychiatric emergency department in Barcelona seem to show significant meteorotropism.

	Any Anxiety Days			**Panic Anxiety Days**			**Non-panic Anxiety Days**		
Variables	**OR**	(95%CI)		**OR**	(95%CI)		**OR**	(95%CI)	
Poniente Wind	**1.23**	0.66	2.36	**3.32**	1.76	6.34	**0.60**	0.30	1.15
Saturday-Sunday	**0.69**	0.43	1.09	**0.92**	0.55	1.52	**0.55**	0.34	0.89
Autumn	**1.63**	0.99	2.72	**1.67**	1.00	2.77	**1.40**	0.86	2.27
Rain	**0.78**	0.49	1.26	**0.55**	0.31	0.93	**0.94**	0.58	1.51
Whole Model p	0.11			0.0003			0.035		

Table 6. Odds ratio for days with anxiety (all, panic and non panic), through logistic regression models [47].

On the whole, the results show a higher meteorological sensitivity in patients suffering from panic disorder. In these patients, warm wind increases the risk by three, rain onset reduces it to one-half, and autumn increases it by one and a half. This is not observed in non-panic anxiety, where meteorological effects were not found to be significant.

6. 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 [48] 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. It is plausible that the autonomic nervous system of patients with JHS might be overeactive to some environmental stimuli like the weather.

However, under the "modern" name dysautonomia not only anxiety features can be found [49] but also many symptoms described for more than two centuries in the present group of anxiety disorders [50]. 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.

In this sense, Eccles et al. have studied associations between regional cerebral grey matter and hypermobility in healthy volunteers. They found that bilateral amygdala volume distinguished those with hypermobility from those without it. Their data implicate the amygdala as a likely neural substrate mediating previously reported clinical associations between hypermobility, anxiety and psychosomatic conditions. Anxiety is linked theoretically to the abnormal generation and mapping of bodily arousal through the engagement of amygdala and insula. Enhanced interoceptive sensitivity also points to a more finely tuned sensory representation of internal bodily signals within the hypermobile group. Finally, they suggest that hypermobility is a multisystem phenotype that could mediate clinical vulnerability to neuropsychiatric symptoms [51]. Therefore, the link between JHS and dysautonomia provides 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 co-

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morbidity 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.

7. 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 an interstitial duplication of human chromosome 15 (named DUP 25) as responsible for this association (with a non-Mendelian mechanism of disease-causing mutation) 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, osteomuscular, irritable bowel, hypo/hyperthiroid, 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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