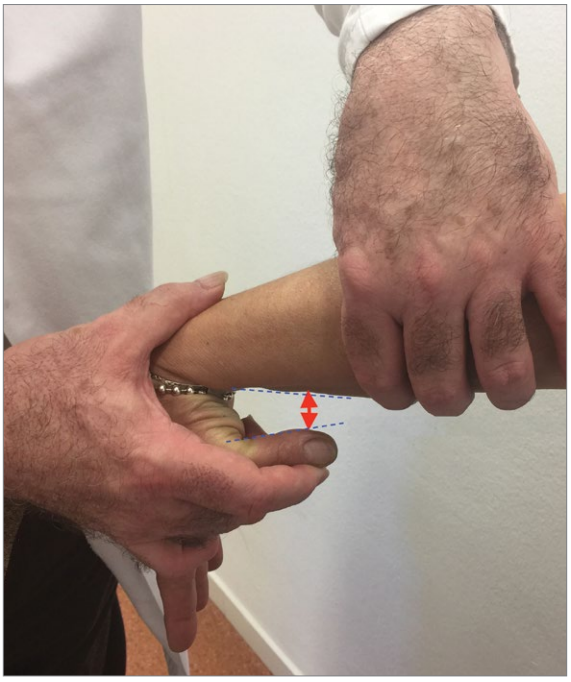
Current PSYCHIATRY

# Anxiety and joint hypermobility: An unexpected association

## Examining this link can improve diagnosis and treatment of both disorders



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Joint hypermobility syndrome (JHS)—also known as Ehlers-Danlos type 3–hypermobile type (hEDS)[1]—is a poorly recognized connective tissue disorder characterized by increased joint laxity that may affect 10% to 25% of the general population.[2] Researchers are increasingly recognizing an association between JHS/hEDS and psychiatric symptoms and disorders, specifically anxiety. In this review, we describe the clinical presentation of JHS/hEDS, propose a new "Neuroconnective phenotype" based on the link between anxiety and JHS/hEDS, and discuss factors to consider when treating anxiety in a patient who has JHS/hEDS.

### JHS/hEDS: A complex disorder

Although JHS/hEDS is a heritable condition, several factors are known to influence its prevalence and visibility, including age, sex, and ethnicity; the prevalence is higher among younger patients, females, and African Americans.[2] Its known basis is the type and distribution pattern of collagen, and one of the key features used to identify this syndrome is greater joint laxity, meaning increased distensibility of the joints in passive movements as well as a hypermobility in active movements.

Although first described by two dermatologists (Edvard Ehlers and Henri-Alexandre Danlos) at the beginning of the 20th century, JHS/hEDS is now considered a multisystemic condition. Thus, JHS/hEDS includes a wide range

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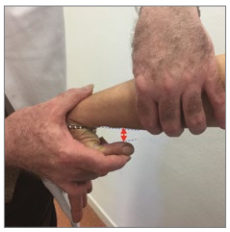

**Anxiety and joint hypermobility**

**Clinical Point**

**JHS/hEDS has been associated with increased fears and greater anxiety severity**

Table

## Musculoskeletal and extra-articular features of JHS/hEDS

| Category | Features |
|---|---|
| Musculoskeletal | Joint: Joint laxity, arthralgia/myalgia, dislocation/subluxation, osteoarthritis, chondromalacia patellae, temporomandibular joint dysfunction, pain |
| | Soft tissue: Ligament/muscle/meniscus tear, epicondylitis, bursitis, tendinitis, capsulitis, Baker cysts |
| | Spine: Disc prolapse, loose back syndrome, spondylolysis, spinal abnormalities, spinal stenosis, scoliosis |
| Extra-articular | Neurologic: Dysautonomia, headache, chronic regional pain syndrome, carpal tunnel syndrome, developmental coordination disorder, fixed dystonia |
| | Gastrointestinal: Visceroptosis, irritable bowel syndrome, gastroesophageal reflux, hiatus hernia, chronic constipation, rectal evacuatory dysfunction, functional gastrointestinal disorder, Crohn's disease, oropharyngeal dysphagia |
| | Mucosa: Blue sclera, xerostomia, xerophthalmia, vaginal dryness, agenesis/absence of the lingual frenulum, mucosal fragility (with subsequent spontaneous bleeding) |
| | Urologic: Urinary stress incontinence |
| | Gynecologic: Pelvic organ prolapse, irregular menses, meno/metrorrhagias, dysmenorrhea |
| | Psychiatric: Anxiety, depression, eating disorders, psychological distress |
| | Skin: Skin hyperextensibility, hypertrophic scarring, skin fragility, striae, easy bruising (capillary fragility), atopy |
| | Cardiovascular: Mitral valve prolapse, postural tachycardia syndrome, Chiari malformation, aortic valve regurgitation |
| | Others: Fibromyalgia, chronic fatigue syndrome, somatosensory amplification, increased interoception and exteroception, decreased proprioception |

JHS/hEDS: joint hypermobility syndrome/Ehlers-Danlos type 3–hypermobile type

**Source:** References 2,5,6

of musculoskeletal features, and over the recent years, extra-articular symptoms, such as easy bruising or hypertrophic scarring, have gained recognition.[3] Moreover, individuals with JHS/hEDS frequently present with stress-sensitive illnesses, such as fibromyalgia, or chronic fatigue syndrome.[4] The ***Table***[2,5,6] provides a description of musculoskeletal and extra-articular features of JHS/hEDS.

## The link between JHS/hEDS and anxiety

Psychiatric symptoms are being increasingly recognized as a key feature of JHS/hEDS. Our group published the first case control study on the association between JHS/hEDS and anxiety in 1988.[7] Additional studies have consistently replicated and confirmed these findings in clinical and nonclinical populations, and in adult and geriatric patients.[8-12] Specifically, JHS/hEDS has been associated with a higher frequency and greater intensity of fears, greater anxiety severity and somatic concerns, and higher frequency of the so-called endogenous anxiety disorders.[6,13] There also is limited but growing evidence that JHS/hEDS is associated with depressive disorders, eating disorders, and neurodevelopmental disorders as well as alcohol and tobacco misuse.[6,8,11,14,15]

**Moving toward a new phenotype.** Whereas there is increasing evidence of somatic comorbidity in several major psychiatric disorders, present psychiatric nosology does not include specific psychiatric illnesses associated with medical conditions other than organic dementias and secondary psychiatric conditions. However, the overwhelming data on clinical comorbidity (both somatic and psychiatric) require new nosologic approaches. Following the accumulated evidence on this topic over

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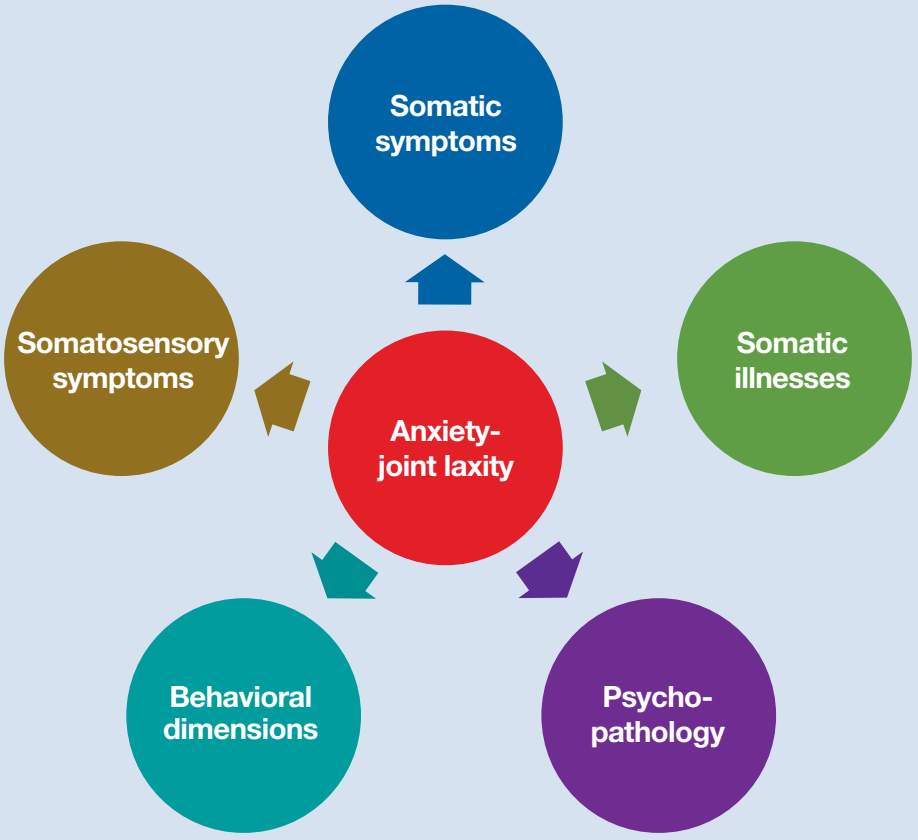
Figure 1

## The Neuroconnective phenotype: 5 Dimensions




**Somatic symptoms** include dysautonomia, asthenic somatotype, blue sclera, "easy bruising," eczemas, dyskinesia, dislocations, prolapses, and hypertrophic scars. **Somatic illnesses** include irritable bowel syndrome, dysfunctional esophagus, chemical sensitivities, dizziness, fatigue, fibromyalgia, "dynias," hypothyroidism, asthma, migraines, temporomandibular dysfunction, and food intolerance. **Psychopathology** includes increased interoception, exteroception, decreased proprioception, anticipatory anxiety, phobias, mood symptoms, eating disorders, neurotic personality traits, neurodevelopmental disorders, high sensitivity to loss, and high positive confrontation. **Behavioral dimensions** are patterns of defense mechanisms that often are identifiable at the extreme of a continuous axis (ie, fight/flight, avoidance/dependency). **Somatosensory symptoms** include increased olfactory sensitivity, eye-contact difficulty, selective photophobia, dyspnea, dysphagia, choking, palpitations, joint pain, and enhanced sensitivity to weather and chemicals.

**Clinical Point**

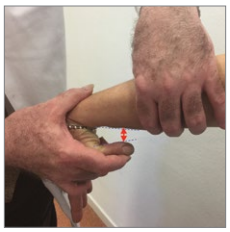
**The core of the 'Neuroconnective phenotype' is an association between joint laxity and anxiety**

the past 30 years, our group described the "Neuroconnective phenotype" (***Figure 1***) on the basis of the collected genetic, neurophysiological, neuroimaging, and clinical data.[6] The core of the phenotype includes the "anxiety-joint laxity" association and has 5 dimensions that allow for minor overlap (somatic symptoms, somatic illnesses, psychopathology, behavioral dimensions, and somatosensory symptoms). Each of the 5 dimensions includes features that may be present at different degrees with individual variations.

Biologic hypotheses that have been proposed to explain the link between anxiety and JHS/hEDS are described in the ***Box***[6,16-28] (***page 18***).

## How JHS/hEDS is diagnosed

The Beighton criteria are the most common set of criteria used to diagnose JHS/hEDS.[29] In 2000, Grahame et al[30] developed the Brighton criteria, which include some extra-articular features. The "Hospital del Mar" criteria[31] (also known as the "Bulbena



**Anxiety and joint hypermobility**

**Clinical Point**

**Atypical body awareness is a feature of multiple disorders, including anxiety and JHS/hEDS**

criteria") were obtained after a multivariate analysis of margins from the Beighton criteria and the original set of criteria described by Rotés. They showed consistent indicators of reliability, internal consistency, and better predictive validity.[31]

Recently, several self-assessment questionnaires have been developed. Specifically, based on the Hakim and Grahame questionnaire,[32] our group developed a novel self-assessment questionnaire that includes pictures to facilitate the diagnosis.[33]

However, despite multiple ways of assessing JHS/hEDS, it remains mostly undiagnosed and untreated. Because of this, a new clinician-administered checklist has been developed,[34] although this checklist does not include the psychiatric aspects of the disorder, so clinicians who use this checklist should ensure that the patient receives additional psychiatric assessment.

## Transforming the clinical value into specific interventions

Anxiety disorders are chronic, disabling, and represent the 6th leading cause of disability worldwide.[35] They have a significant impact due to the high cost of frequent medical evaluations and treatment of the physical components of the disorder.[36] As a clinical marker for a homogeneous type of anxiety, JHS/hEDS can provide valuable information about a patient's complete clinical picture, especially about the somatic aspects of the disorder.

No randomized controlled trials have been conducted to evaluate pharmacotherapy as treatment for JHS/hEDS. In a cohort study, the overall use of psychotropics was significantly higher in patients with JHS/hEDS compared with controls.[37] Anxiety symptoms often are treated with antidepressants, and patients with JHS/hEDS

**Box**

### What underlying mechanisms link anxiety and joint hypermobility?

Interestingly, both anxiety and joint hypermobility syndrome/Ehlers-Danlos type 3–hypermobile type (JHS/hEDS) are often underdiagnosed and undertreated, and have similar prevalence in the general population. While it is possible that some psychiatric symptoms can be a consequence of adaptation and difficulties in dealing with chronic illnesses, biologic hypotheses have been considered to explain the association between JHS/hEDS and anxiety. The most accepted biologic hypotheses include:

- genetic risks
- interoceptive sensitivity
- somatosensory amplification
- emotion processing variances
- autonomic nervous system dysfunction.

A duplication of chromosome 15 (DUP-25) was found in patients with both JHS/hEDS and an anxiety disorder,[16] but to date, this finding has not been replicated.[17,18] The fact that both conditions are highly heritable suggests high likelihood of a genetic linkage. Other theories about the neural connections between mind and body have been proposed. Brain and body are intrinsically and dynamically coupled; perceptions, emotions, and cognitions respond to and change the state of the body.[19] In this sense, body perception and dysautonomia have gained recognition.

Patients with JHS/hEDS have higher interoception,[20] meaning greater signaling and perception of internal bodily sensations. This is in line with Critchley's hypothesis, in which he describes the influence of visceral inputs over thoughts, feelings, and behavior.[21] Consistent with Critchley's views, Porges described the Polyvagal Theory,[22] which is phylogenetic approach relating the autonomic nervous system to behavior. Atypical body awareness is a feature of multiple disorders, including anxiety, depression, and JHS/hEDS.[19,23-25] Interestingly, a recent neuroimaging study found that interception sensitivity mediated the relationship between anxiety and hypermobility.[20]

JHS/hEDS patients have greater exteroception (perception of environment), nocioception (pain perception), and somatosensory amplification.[6,26] At the same time, they also have decreased proprioception,[27] which could explain the coordination difficulties they experience. Neuroimaging studies have confirmed that individuals with JHS/hEDS have structural differences in key emotion processing regions, notably affecting the amygdala bilaterally.[28]

Together, these findings increase our understanding about the mechanisms through which vulnerability to anxiety disorders and somatic symptoms arises in certain patients.

are extremely sensitive to adverse effects. Particularly at the beginning of treatment, they may feel uneasy and restless, and have significant gastrointestinal symptoms, which can exacerbate their anxiety symptoms. Because the anticholinergic effects of tertiary tricyclic antidepressants can reduce abdominal pain and improve bowel movements, this class of medication should be considered. The likelihood of success is greater if medications are started at low doses and are titrated extremely slowly.

Current nosology of anxiety disorders neglects the somatic aspects and physical manifestations of anxiety, and in general, therapeutic interventions focus only cognitive/psychological aspects of anxiety. Cognitive-behavioral therapy (CBT) may be effective in treating the cognitive distortions associated with the chronicity of the illness and negative emotions. Baeza-Velasco et al[38] found that patients with JHS/hEDS have a tendency toward dysfunctional coping strategies, and CBT may be useful to address those symptoms. Moreover, these individuals often suffer from kinesiophobia and hyperalgesia. Some pilot CBT strategies have been developed, and research suggests that along with exercise, CBT can be a valuable pain management tool in patients with JHS/hEDS.[39]

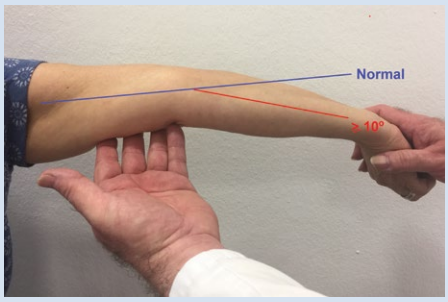
Nonetheless, these patients often suffer from several somatic complaints and bodily manifestations (eg, somatosensory amplification, dysautonomia) that require treatment. Thus, interventions that address mind and body connections should be implemented. Some research found meditative therapies for anxiety disorders can be effective,[40,41] although further randomized controlled trials are needed.

Based on our proposed "Neuroconnective phenotype," we suggest a new therapeutic approach to address the 5 dimensions of this phenotype.

**Somatic symptoms**, such as blue sclera, dislocations, scars, easy bruising, and leptosomatic somatotype, do not require specific intervention, but they provide information about the physical phenotype of JHS/hEDS and can facilitate the diagnosis.

Figure 2

## Elbow hyperextension




Hyperextension of the elbow (10°) beyond the regular range of motion

**Somatic illnesses.** Treatment must address often-found comorbid medical conditions, such as irritable bowel syndrome, other gastrointestinal conditions, temporomandibular dysfunction, fatigue, fibromyalgia, and dysautonomia. Obviously specific attention must be paid to JHS/hEDS, which responds relatively well to physical treatments, including aerobic exercise, and particularly well to expert physiotherapy. Relaxation and meditation techniques also are effective.

**Psychopathology.** Ensure proper assessment and treatment not only of the anxiety disorder and its dimensions (ie, anticipatory anxiety, high loss sensitivity, depersonalization, impulse phobias, or avoidance behavior), but also of the other related conditions, such as mood disorders, substance use disorders, or eating disorders.

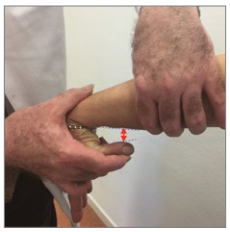
**Behavioral dimensions.** Defense mechanisms often take individuals with JHS/hEDS to the extremes of a circumflex behavioral model in which the most typical axes include the following: me/others, loss/excess of control, avoidance/invasion, fight/flight, and dependency/isolation. A rich psychotherapeutic approach that focuses on these defense mechanisms and behavioral axes is required to balance these mechanisms.

**Somatosensory symptoms.** Be aware of, validate, and provide understanding of the



**Clinical Point**

**Patients with JHS/hEDS may be extremely sensitive to adverse effects of antidepressants used to treat anxiety**



**Anxiety and joint hypermobility**

## Related Resources

- Bulbena A, Baeza-Velasco C, Bulbena-Cabré A, et al. Psychiatric and psychological aspects in the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175(1):237-245.
- The Ehlers-Danlos Society. hEDS Diagnostic Checklist. https://www.ehlers-danlos.com/heds-diagnostic-checklist/.

patient's increased sensitivities, including greater pain, body perception, meteorosensitivity, and higher sensitivity to medications and adverse effects.

**Clinical Point**

**CBT may be useful to address dysfunctional coping strategies in patients with JHS/hEDS**

## Additional research is needed

Future directions for exploring the link between anxiety and JHS/hEDS should include the development of new nosologic approaches, the expansion of the therapeutic dimension, and unmasking the common biologic mechanisms using evolutionary models.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# Bottom Line

Recognizing the link between anxiety and joint hypermobility syndrome/Ehlers-Danlos type 3–hypermobile type (JHS/hEDS) has provided a way to better understand psychopathologic and somatic conditions. In patients who present with an anxiety disorder, clinicians should screen for JHS/hEDS to properly evaluate and treat all dimensions of the newly described "Neuroconnective phenotype."

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