ARTICLE

Psychiatric and Psychological Aspects in the Ehlers–Danlos Syndromes

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There is increasing amount of evidence pointing toward a high prevalence of psychiatric conditions among individuals with hypermobile type of Ehlers–Danlos syndrome (JHS/hEDS). A literature review confirms a strong association between anxiety disorders and JHSh/hEDS, and there is also limited but growing evidence that JHSh/hEDS is also associated with depression, eating, and neuro-developmental disorders as well as alcohol and tobacco misuse. The underlying mechanisms behind this association include genetic risks, autonomic nervous system dysfunction, increased exteroceptive and interoceptive mechanisms and decreased proprioception. Recent neuroimaging studies have also shown an increase response in emotion processing brain areas which could explain the high affective reactivity seen in JHS/hEDS. Management of these patients should include psychiatric and psychological approaches, not only to relieve the clinical conditions but also to improve abilities to cope through proper drug treatment, psychotherapy, and psychological rehabilitation adequately coupled with modern physiotherapy. A multidimensional approach to this "neuroconnective phenotype" should be implemented to ensure proper assessment and to guide for more specific treatments. Future lines of research should further explore the full dimension of the psychopathology associated with JHS/hEDS to define the nature of the relationship. © 2017 Wiley Periodicals, Inc.

KEY WORDS: joint hypermobility; anxiety; psychopathology; neuroconnective phenotype; hypermobile Ehlers–Danlos syndrome

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INTRODUCTION

The relationship between the JHS/hEDS and anxiety was an unexpected finding that we first described in 1988 at the Hospital del Mar in Barcelona [Bulbena et al., 1988]. It really was a clinical observation rather than a pathophysiological reasoning and the reiterated coincidence of the two conditions prompted us to study this association in more detail. Prior to this study, there were some scattered observations in the literature pointing to this new direction. In 1957, rheumatologist Rotés-Querol and Argany [1957] observed a remarkable degree of nervous tension suffered by patients with hypermobility. To a certain extent, there were some indirect references about the relationship between "visceroptosis" and anxiety/phobias in the classical psychosomatic literature [Flanders Dunbar, 1955].

Literature uses indistinctly Joint Laxity (the original name), Joint Hypermobility (the given name) and Elher–Danlos Syndrome-Hypermobile type (hEDS). Joint hypermobility (JH) is characterized by an extended range of motion of the joints, increased distensibility of joints in passive movements and hypermobility in active movement in the absence of another rheumatologic disease. JHS/hEDS is multisystem condition associated with musculoskeletal dysfunctions, possibly resulting from a glycoprotein deficiency and genetic alterations affecting the formation of collagen, which would explain tissue looseness, prolapsed organs, visceroptoses, pneumotorax, and vulnerability to trauma in these patients.

There are several sets of criteria that show minimal variations from the originally proposed by Rotés, although new self-assessment questionnaires have been added to the assessment methods of JHS [Hakim and Grahame, 2003; Bulbena et al., 2014]. A review paper of all the available criteria showed a high degree of agreement among all of them [Bulbena et al., 1992] but a more comprehensive set of 10 criteria obtained by cluster analysis was also proposed. However, the most often used are the "Beighton criteria" converted to a 9-point clinical scale by which subjects with a score ≥ 4 are considered as having JHS. In 2000, Grahame et al. [2000] developed the Brighton criteria to replace the Beighton criteria for the joint hypermobility syndrome (JHS). According to these criteria, the syndrome diagnosis is made taking into account the Beighton score and also some other clinical manifestations associated with hypermobility. The clinical assessment of the JHS/hEDS is not difficult but examiners should be trained in order to ensure the reliability of the exam.

Joint hypermobility (JH) is characterized by an extended range of motion of the joints, increased distensibility of joints in passive movements and hypermobility in active movement in the absence of another rheumatologic disease.

In this article, we review the psychopathology associated with JHS/hEDS, as well as the possible explanations for such association, the controversies, management, and future lines of research.

METHODS

The working group was composed of well-respected international clinician-researchers in the area of psychopathology with special interests in Ehlers–Danlos syndromes as part of the International Consortium on the Ehlers–Danlos Syndromes. Literature searches were conducted using the main electronic databases including the Cochrane Library, Informit, PsycINFO, PubMed, and Scopus. The main search terms used were "joint hypermobility syndrome," "joint hyperlaxity," "anxiety," and each separate psychiatric diagnostic category. Studies were included if they were published until September 2016, either in English or Spanish, if they reported any psychiatric conditions associated with joint hypermobility. The consensus was obtained after all authors completed their contributions and reviewed the manuscript on three separate occasions to ensure general agreement by all the authors. A total of 66 articles were included in the review.

LITERATURE REVIEW

Psychopathology

Herein, the syndromes joint hypermobility syndrome (JHS) and the hypermobile type of Ehlers–Danlos are considered as single entity (JHS/hEDS) for the purposes of this discussion defined by the previous diagnostic criteria, Brighton and Villefranche, respectively, except where the distinction is considered pertinent. See "The 2017 International Classification of the Ehlers-Danlos Syndromes" by Malfait et al., this issue.

Anxiety disorders

The relationship between JHS/hEDS and anxiety disorders has been widely explored during the past 30 years and current literature supports a solid association between these two variables [Bulbena et al., 2015]. Bulbena et al. [1993] conducted the first empirical case-control study where a sample of rheumatologic outpatients with JHS/hEDS were assessed and ~70% of hypermobile patients had some type of anxiety disorder, as compared to 22% in the controls [Bulbena et al., 1988]. A second study [Martin-Santos et al., 1998] evaluated outpatients with new

diagnoses of panic disorder and/or agoraphobia and found that JHS/hEDS was present in ~70% of patients with anxiety disorders compared to 10% in the controls. Garcia Campayo et al. [2010] also found a high prevalence of JHS/hEDS (61.8%) among subjects suffering from panic disorders compared with 10.9% among healthy controls.

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Other studies in non-clinical populations showed that individuals with JHS/hEDS scored significantly higher in state/trait and social anxiety scales [Bulbena et al., 2004; Baeza-Velasco et al., 2011a]. A recent meta-analysis [Smith et al., 2014] revealed that people with JHS/hEDS experience significantly greater perception and fear intensity and have higher probability of agoraphobia and panic disorders. These authors pointed out that current evidence is derived from Mediterranean adult populations and highlighted that more research should be done to study this association in other populations.

The only incidence study that evaluated the relationship between JHS/hEDS and anxiety disorders was done in the general population with a 15 years follow-up [Bulbena et al., 2011]. Cumulative incidence of panic/agoraphobia disorder was significantly higher in the JHS/hEDS group (41.4%) with a relative risk of 22.3 (95% confidence interval [CI] 4.6–108.7, $P < 0.0001$). Incidence of social and simple phobia was also significantly higher in the JHS/hEDS group and anxiolytic drug use was nearly fourfold higher among JHS/hEDS group.

Mood disorders

Some studies examined the relationship between mood disorders and JHS/hEDS but the research on this area is significantly smaller compared to anxiety disorders. Two studies [Bair et al., 2003; Gurer et al., 2010] explored depressive disorders in JHS/hEDS subjects but no differences were found when comorbid anxiety was controlled for. In contrast, Pasquini et al. [2014] observed a higher rate of depressive symptoms in JHS/hEDS patients compared to controls. Other studies also revealed higher depressive symptoms in individuals with joint hypermobility (JH) without a known diagnosis of JHS/hEDS [Baeza-Velasco et al., 2011b; Murray et al., 2013]. The meta-analysis of Smith et al. [2014] concluded that people with JHS/hEDS commonly exhibit more anxiety and depressive symptoms. Hershenfeld et al. [2016] found 42.5% prevalence of psychiatric disorders (especially depression and anxiety) in a retrospective sample of JHS/hEDS subjects. Therefore, some preliminary evidence suggests higher rates of depressive symptoms among JHS/hEDS, especially when comorbid anxiety is present.

Personality disorders

The evidence in the field of personality disorder is very scarce and to date there is only one study published about it. Pasquini et al. [2014] observed that subjects with JHS/hEDS have a 5.8 relative risk of having a personality disorder, particularly anxious obsessive-compulsive personality disorder. Although this is in line with prior research studies that support a strong relationship between anxiety and JHS/hEDS, these results should interpreted with caution due to the lack of large, well-designed studies in this field.

Addictions

Most of the research about addiction in JHS/hEDS focused on substances (alcohol and tobacco mainly) and there are no studies about other dimensions of addiction such as behavioral addiction. Carlsson and Rundgren [1980] found significantly higher joint hypermobility scores among female alcoholic patients but did not diagnose hEDS in these same patients so the relevance is unclear. Interestingly, they proposed a link to hormonal dysregulation in chronic alcoholics to the increase in joint laxity. Lumley et al. [1994] reported that in a sample of EDS patients ($N = 48$; including adults and children and multiple types), 12% were found to have a history of alcohol or illicit drug use although the type of illicit substance was not specified. Since chronic pain was one of the major psychological stressors in that study, it would be interesting to know if there was a misuse of pain medications as well. Regarding tobacco addiction, Carbone et al. [2000] studied the bone density in JHS/hEDS and found that the control group smoked more tobacco and were taller compared to the JHS/hEDS group, which is not consistent with other findings that showed that patients with hEDS have a tendency towards the ectomorphic (thin and tall) phenotype and also that people with hEDS smoke more cigarettes. A longitudinal study found smokers had significantly higher JH scores [Baeza-Velasco et al., 2015a] which was consistent with prior studies. Coping with distress is frequently cited as a motive for the higher tobacco and alcohol use as both substances are known to reduce anxiety.

Eating disorders

Most studies seem to point toward a relationship between ectomorph somatotype (linear, thin, and usually tall) and JHS/hEDS [Bulbena et al., 2015], with higher rates of restrictive or compensatory eating disorders such as anorexia or bulimia. Some case reports described a co-occurrence of EDS and eating disorders such as anorexia nervosa (AN) [Al-Mufty and Bevan, 1977; Miles et al., 2007], although the type of EDS was not specified in the reports. Goh et al. [2013] hypothesized that since there is symptom overlap seen AN and JH such as gastrointestinal symptoms, orthostatic intolerance, and fatigue associated syndromes, JH is a possible

indicator of a familial disorder of connective tissue elasticity which potentially plays a causal role in the development of the eating disorder.

Most studies seem to point toward a relationship between ectomorph somatotype (linear, thin, and usually tall) and JHS/hEDS, with higher rates of restrictive or compensatory eating disorders such as anorexia or bulimia.

Recently, Baeza-Velasco et al. [2015b] proposed a model of eating disorders in JHS/hEDS that provided some light about this phenomenon. The authors hypothesized that both articular and extra-articular features play a role in developing and maintain these eating patterns (Fig. 1).

Psychosis

There are some articles addressing the relationship between JHS/hEDS and schizophrenia. Bulbena et al. [2005] studied 124 patients with schizophrenia with and without comorbid JHS/hEDS and found JHS/hEDS was markedly more frequent within the schizophrenic-panic/phobic cluster (62.1%) [OR: 9.35, CI: 3.85–22.73, $P < 0.0001$]. Similarly, Bulbena et al. [2007] found that individuals with comorbid schizophrenia JHS/hEDS had higher rates of phobia/panic anxiety and more positive symptoms as well, and postulated that JH could be a clinical marker for this phenotype in schizophrenia. In a third case control study (schizophrenic patients vs. healthy controls) done by the same group evaluating the somatotype in schizophrenia, JHS/hEDS had comparable rates between the groups but there was a tendency toward positive association between anxiety-joint hypermobility and anxiety-ectomorphism [Pailhez et al., 2009]. A case report by Sienaert et al. [2003] described a case where a patient with comorbid schizoaffective disorder and classical EDS received electroconvulsive therapy, although it is unclear if the patient met diagnostic criteria for classical EDS.

Neurodevelopmental disorders

This is a burgeoning area of research that has developed over the recent years which seems to indicate a degree of co-occurrence of JHS/hEDS and some neuro-developmental disorders including attention-deficit/hyperactivity disorders (ADHD), developmental coordination disorder (DCD), and autism spectrum disorder (ASD).

In the area of ADHD, Eccles et al. [2014] found that adults with ADHD had higher rates of JH and symptoms of autonomic dysfunction compared to healthy controls. Another study, done by Harris [1998] that was published as a letter to the editor, found that the great majority (99%) of children with ADHD in his sample had JH, although this results should be interpreted with caution as it is based on clinical observations with no methodology reported. Similarly, Hollertz [2012]

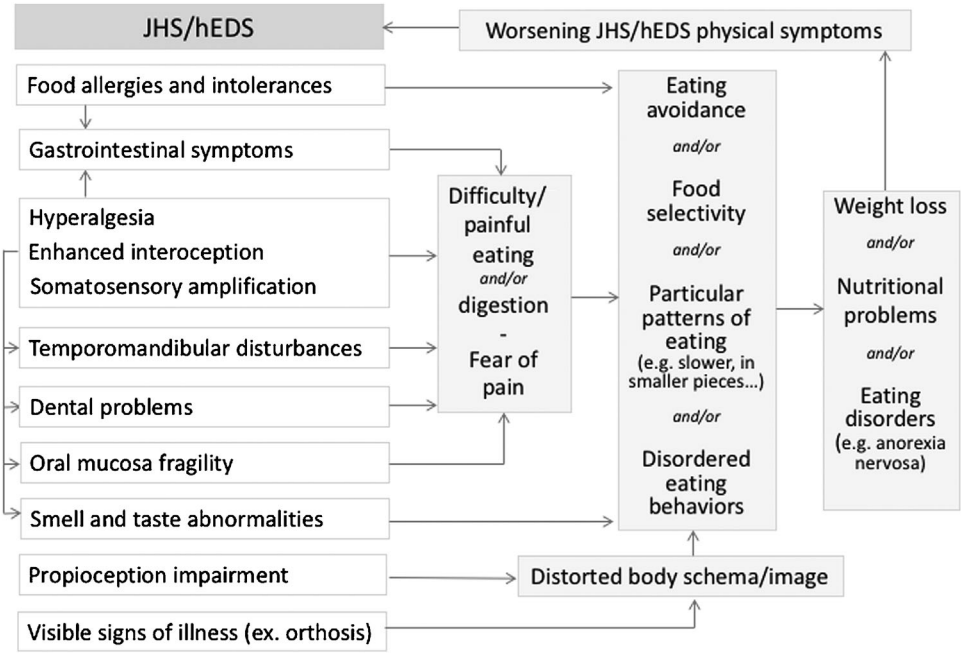


Figure 1. This figure reflects different extra-articular features such as gastrointestinal problems, temporomandibular disorders, and food intolerances that contribute to developing and maintaining disturbed eating behaviours and significant weight loss seen JHS/hEDS patients. See "Hypermobile Elhers-Danlos Syndrome (a.k.a. Ehlers-Danlos Syndrome type III and Ehlers-Danlos Syndrome Hypermobility Type): Clinical Description, and Natural History" by Tinkle et al., in this issue.

reported high co-occurrence of EDS and ADHD based on an observational study. Other authors such as Dogan et al. [2011] and Shiari et al. [2013] did matched case control studies and found that JH was significantly higher in the ADHD group as well as anxiety compared to healthy controls.

Concerning DCD, Kirby and Davies [2007] reported that children with DCD have more symptoms associated with JHS/hEDS including joint hypermobility, pain, and autonomic dysfunction compared to asymptomatic typically developing children. Jelsma et al. [2013] found a significantly higher mean score of JH in the DCD-group as compared to age-matched, typically developing children. Ghibellini et al. [2015] suggested that the relationship between JH and DCD may be due to poor proprioception in hypermobile children.

No articles are published regarding the relationship between ASD and JHS/hEDS but a few have looked at the prevalence of JH in ASD. Shetreat-Klein et al. [2014] did a matched case control study and found that ASD children have greater mobility of joints and more gait abnormalities compared to healthy controls. However, this study had a relatively small sample and excluded children with overt neurological problems, which may not be an accurate representation of the ASD population. Also, few case reports also highlighted the comorbidity ASD–JH [Tantam et al., 1990; Sieg, 1992; Takei et al., 2011], but further studies need to further explore the possible association of JHS/hEDS and ASD.

Psychiatric and Psychological Treatment for hEDS

Although no specific studies about psychopharmacologic treatment for hEDS have been published yet, there is significant evidence that JHS/hEDS patients take more anxiolytics than the counterpart. The overall use of psychotropic drugs was 41.4% in JHS/hEDS subjects compared to 13.9% in controls (OR: 4.38 CI 95% 1.8–10.9) [Bulbena et al., 2011].

Although no specific studies about psychopharmacologic treatment for hEDS have been published yet, there is significant evidence that JHS/hEDS patients take more anxiolytics than the counterpart. The overall use of psychotropic drugs was 41.4% in JHS/hEDS subjects compared to 13.9% in controls (OR: 4.38 CI 95% 1.8–10.9).

High levels of anxiety and depression are frequent in JHS/hEDS [Smith et al., 2014; Bulbena et al., 2015] and it has been shown that negative emotions may increase the experience of pain [Linton and Shaw, 2011]. Celletti et al. [2013] observed that patients with a JHS/hEDS had high scores of kinesiophobia. JHS/hEDS patients also have hyperalgesia [Castori, 2013], enhanced interoception [Mallorqui-Bague et al., 2014; Bulbena et al., 2015], and a tendency toward a somatosensory amplification [Baeza-Velasco et al., 2011b]. These aspects related to increased perception and/or reduced tolerance of pain [Feuerstein and Beattie, 1995; Pollatos et al., 2012], might influence the pain experience.

Dysfunctional coping strategies were also associated with JH [Baeza-Velasco et al., 2015a]. However, there are no studies exploring the coping strategies in JHS/hEDS and psychological aspects of pain perception merits more research to develop treatments programs. Some pilot cognitive behavioral therapy (CBT) experiences have been developed and suggested that CBT is valuable in the pain management of JHS/hEDS patients [Bathen et al., 2013].

Possible etiologies

Although it is possible that some psychiatric symptoms, risk or defensive behaviors, and personality traits can be a consequence of adaptation and difficulties in dealing with chronic illnesses, biological hypotheses have been considered to explain this association [Baeza-Velasco et al., 2015a]. The genetic link between anxiety and hyperlaxity should be further explored. In this sense, Gratacos et al. [2001] reported a cytogenetic anomaly (DUP-25) common to these two phenomena, although to date this study has not been replicated [Tabiner et al., 2003; Henrichsen et al., 2004]. Eccles et al. [2012] observed structural differences in areas of the brain implicated in emotion regulation in JHS.

Moreover, dysautonomia presents with symptoms that overlap with anxiety disorders. The perception/interpretation of physiological excitation play a role in anxiety disorders [Clark, 1986; Damasio, 1996; Craig, 2003] and JHS/hEDS patients have more intense interoception [Mallorqui-Bague et al., 2014] and are more likely to experience somatosensory amplification [Baeza-Velasco et al., 2011b]. Using multiple regression analysis, both JHS/hEDS and anxiety disorders were independently related to body perception and somatosensory amplification.

The Polyvagal Theory, proposed by Porges [2012], suggests that the evolution of the mammalian autonomic nervous system provides the neurophysiological substrates for adaptive behavioral strategies in both safe and dangerous environments. The theory provides a model to investigate the circuits that may be involved in dysautonomia and how atypical neural regulation of the autonomic nervous system that may function as a neural platform for several of the features observed in JHS/hEDS. Based on the Polyvagal theory [Porges and Furman, 2011], the Body Perception Questionnaire [Porges, 1993] has been applied to objectively quantify subjective reports of bodily reactions and states. The questionnaire identified atypical profiles in JHS/hEDS [Bulbena et al., 2014] and is being validated for clinical use.

In another study, trait anxiety scores did significantly correlate with both state anxiety and hypermobility

scores. Hypermobility scores were also associated with other key affective processing areas in the whole brain analysis [Mallorqui-Bague et al., 2014, 2015, 2016]. These findings increase our understanding of emotion processing in JHS/hEDS people and the mechanisms through which vulnerability to anxiety and somatic symptoms arises in this population.

Another physiological fact that may underlie this relationship is the strong value of the visceral afferent signals to the brain. This has been extensively studied by Critchley et al. [2013] who showed how different visceral inputs can influence thoughts, feelings, and behavior.

Considering the growing evidence of enhanced body awareness among JHS/hEDS along with the increased interception and somatosensory amplification, there might be an excess of alarming information which leads to psychological discomfort and psychiatric conditions.

Controversies

There are some controversies regarding the psychopathology associated with JHS/hEDS that should be addressed. First, patients with chronic pain and decreased functionality often display anxiety and depression [Bair et al., 2003], independently of the hEDS diagnosis. Another point is that hEDS is associated with multiple conditions like dysautonomia, which can cause a broad spectrum of physical complaints that can mimic anxiety-like symptoms. For instance, patients with dysautonomia experiencing intense heart rate fluctuations could be misdiagnosed with panic attacks. Another example could be the extreme fatigue caused by poor sleep architecture seen in these patients, that could be mistaken as depression. The key lies in being able to identify the cause of the anxiety and depression—if it is centrally mediated as a behavioral disorder or if it is the manifestation of associated conditions.

Another controversy in hEDS lies in diagnosing children or their parents with Conversion Disorder or Munchausen by Proxy respectively. These children often present with chronic pain, easy bruising, multiple joint dislocations, abdominal pain, dizziness, and fatigue that can be misdiagnosed as Conversion Disorder or Munchausen by Proxy. Barnum [2014] recently published a case of a child who had EDS but was misdiagnosed with conversion disorder and highlighted the stigmatizing consequences of making the wrong diagnosis in this population.

It is crucial that the physicians making the psychological assessment of hEDS patients are appropriately trained with the articular and extra-articular symptoms.

Management

The psychiatric and psychosocial issues have to be explored and properly evaluated in these patients. Pain, negative feelings, and poor emotion regulation are frequently associated with this condition. The consideration of all these aspects can help develop adapted protocols of evidence based psychiatric treatment and psychosocial interventions such as CBT (Table I).

Future lines of research

First, a comprehensive model of illness is needed; the single "medical specialty"

TABLE I. Roles of the Mental Health Professionals in the Management of JHS/hEDS

Objective/problem	Professional/intervention
Psychopathology (anxiety/mood disorders), Associated mental disorders (e.g., Addictions, sleep disorders, etc.)	Psychiatrist (diagnostic and treatment issues) Clinical/health psychologist (CBT) (psychotherapy with or without pharmacotherapy)
Management of chronic pain and negative emotions	Clinical/health psychologist (cognitive-behavioral approach: CBT). Psychiatrist Psychiatric nurse Occupational therapist
Improve knowledge about disease	Therapeutic patient education (pluridisciplinary)
Improve/develop competences to manage chronic disease (e.g., self-efficacy, coping strategies, etc.)	Clinical/health psychologist (CBT). Psychiatric nurse Occupational therapist
Neurodevelopmental disorders in childhood	Child/developmental psychiatrist Child/developmental psychologist (CBT)
Cognitive impairments (attention, memory, etc.)	Neuropsychologist
Support	Clinical psychologist (supportive therapy, different approaches) Psychiatric nurses, OT

This table defines the different r*oles of the mental health professionals in the management of* JHS/hEDS. The objective or problematic areas are introduced in the left column and the proposed intervention in the right column.

approach has to change for a multidisciplinary one. Models including both somatic and also psychiatric/psychological characteristics are required. A first approach was made through the ALPIM spectrum proposal, which is the acronym for anxiety and the domains of its most commonly occurring comorbidities: JHS/hEDS, pain disorders, immune disorders, and mood disorders [Coplan et al., 2015]. The authors of this study hypothesized that the ALPIM syndrome have predictable psychiatric and medical comorbidities and found that significant associations between joint hypermobility and bipolar III, headache with bipolar II, and bipolar II with chronic fatigue syndrome.

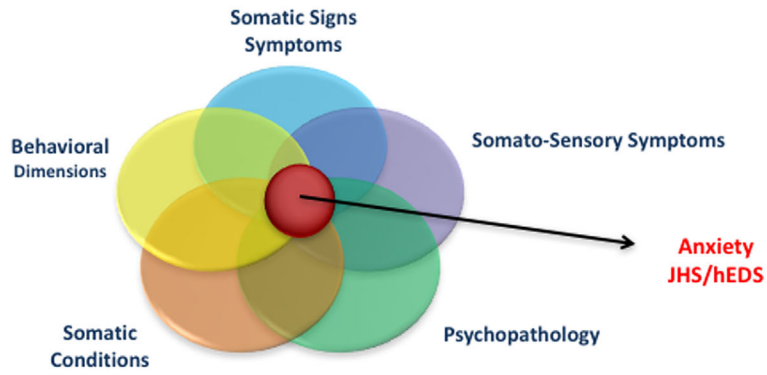
A more recent proposal is the "Neuroconnective phenotype" (Fig. 2), in which, around a common core Anxiety-hEDS, it includes five dimensions: behavioral, psychopathology, somatic symptoms, somatosensory symptoms, and somatic illnesses.

Second, research on the underlying mechanisms is necessary, particularly to unmask the obvious but still occult genetic links. The DUP 25 in the chromosome 15 found among subjects suffering from both anxiety and JHS/hEDS [Gratacos et al., 2001], could not be replicated but it might be worthwhile to further investigate the possible genetic link with new genetic techniques such as whole genomic analyses. The psychophysiological circuits involved between the core features of JHS/hEDS (namely pain and body awareness) and their psychiatric correlates need to be uncovered. These neural correlates may also provide clues to unveil the emotional dysregulation found in JHS/hEDS.

Third, combined treatments tackling both somatic and psychological features should be developed and tested for better evidence based treatments. When talking about phenotypes in psychiatry, authors tend to include only behavioral and psychopathological traits, which again, represents a bias against somatic or body characteristics. Such restrictive view prevents the development of more comprehensive treatments. However, anxiety cases with JHS/hEDS tend to show more somatic features and therefore, it would be worthwhile exploring and developing more specific treatments for them.

Fourth, comprehensive models of care taking a multidisciplinary approach should be implemented. Several experiences, particularly in England, where there is the London Hypermobility Unit at the Hospital of St. John and St. Elizabeth, may be the prototypical model.

Fifth, considering the evidence of the increased risk associated with JHS/hEDS to develop anxiety disorders, preventive strategies particularly among children should be tested and implemented. This may help to guide for more specific treatments and to avoid undesirable outcomes in the adulthood. However, while the link between



- Behavioral Dimensions are patterns of defensive mechanisms that are often identifiable at the extreme of a continuous axis (i.e fight/flight, restriction (avoidance)/dependency
- Somatic symptoms include dysautonomia, asthenic somatotype, "blue " sclera*, "easy bruising", eczemas*, dyskinesia, dislocations, prolapses and hypertrophic scars*
- Somatic Conditions: irritable bowel syndrome, dysfunctional esophagus, chemical sensitivities, dizziness, fatigue, fibromyalgia, -dynias, hypothyroidism, asthma, migraines, temporomandibular dysfunction and food intolerances.
- Psychopathology: increased interoception, exteroception, decreased proprioception, anticipatory anxiety, high loss sensitivity, and high positive confrontation.
- Somato-sensory symptoms include increased olfactory sensitivity, eye-contact difficulty, selective photophobia, dyspnea, dysphagia, choking, palpitations, joint pain and enhances sensitivity to weather and chemicals

* *These features have been previously described in the Neuroconnective phenotype*

Figure 2. The Neuroconnective phenotype. The Neuroconnective model is a proposal that may be useful for clinical practice disorders and of some psychosomatic conditions. It was described after the study and careful consideration of clinical and nonclinical data, pathophysiological mechanisms and the present anxiety nosological status. It is built around the core association of Anxiety-JHS/hEDS and it includes behavioral, psychopathology, somatic symptoms, somatosensory symptoms, and somatic illnesses dimensions. Each of the five dimensions includes features that may be present at different degrees and with individual variations and all dimensions incorporate patterns, clinical symptoms, signs and illnesses seen in these patients.

JHS/hEDS and anxiety disorders has been well established, there is limited evidence regarding the other dimensions of the JHS/hEDS psychopathology that should be further addressed in subsequent studies.

CONCLUDING REMARKS

To conclude, patients with JHS/hEDS often suffer from anxiety disorder and the link between these two variables has been repeatedly found in the literature. There is limited literature about other dimensions of the JHS/hEDS psychopathology that should be further addressed in subsequent studies.

In any case, a more careful psychiatric and psychological approach should be taken along other physical treatments to manage and treat this multisystem condition. A new model described as the Neuroconnective phenotype is proposed to evaluate the different dimensions of the pathology associated including behavioral patterns, clinical symptoms, and related illnesses

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