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Review Article

Joint Hypermobility Syndrome: A Narrative Review

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Abstract: Joint hypermobility syndrome (JHS) is a complex connective tissue disorder characterized by excessive joint mobility and chronic musculoskeletal pain. The condition extends beyond the joints and can affect various systems such as the skin, gastrointestinal tract, neurological system, and cardiovascular system, necessitating a multidisciplinary approach to optimize care. Notably, the prevalence of JHS is higher in young individuals, females, and those of Asian descent. Despite being a common condition, JHS is frequently underdiagnosed, resulting in persistent pain and disability. In order to diagnose JHS, it is necessary to rule out the presence of any consistent feature that indicates the existence of other connective tissue disorders that partially overlap with it, including Marfan and Ehlers-Danlos syndromes. A thorough clinical assessment, coupled with the application of the Brighton Criteria, can aid in making an accurate diagnosis. Management of JHS poses significant challenges and typically involves symptomatic treatment, including physiotherapy, rehabilitation, and pharmacological therapy. Additionally, a multidisciplinary approach, including collaboration with different specialists, is vital. Further research is needed to improve our understanding of JHS and develop interventions based on solid evidence. However, with comprehensive management strategies, individuals with JHS can achieve better pain control and improved function, enabling them to lead more fulfilling lives.

Keywords: Hypermobility Syndrome, Ehlers-Danlos Syndrome, Joint Pain, Chronic Pain

1. Introduction

Joint hypermobility syndrome (JHS) is a heritable connective tissue disorder characterized by hyperextensibility of joints and chronic musculoskeletal pain. This condition affects the articulations of all four limbs and the axial skeleton [1]. However, systemic complaints, such as dysautonomia, fatigue, affective disorders, and gastrointestinal manifestations, are also commonly reported [2, 3]. Despite having a prevalence similar to that of other rheumatologic diseases such as fibromyalgia, gout, and rheumatoid arthritis, JHS is often underdiagnosed [4, 5]. In this narrative review, we will discuss the diverse manifestations of JHS, along with epidemiological aspects, pathophysiological mechanisms, diagnostic approaches, and treatment practices.

2. Epidemiology

Generalized joint hypermobility refers to an extraordinary flexibility in joint movements that affects both large and small peripheral joints, as well as the spine [6]. This condition has a significant genetic component, with a heritability estimate of 70% in females based on a twin study [7]. It is a multifactorial trait that can affect individuals of all genders, with prevalence rates ranging between 6% to 57% in women and 2% to 35% in men, and these rates can vary depending on age and ethnicity [8, 9].

JHS is more common in women. Among individuals of different ethnic origins, the highest prevalence of the condition is seen in individuals of Asian descent, followed by those of African and European descent, respectively. It can affect individuals of all age groups, with milder forms typically occurring in older patients, while more severe cases are often seen in younger individuals. In pediatric patients, JHS is present in 10 to 15% of children with chronic pain syndrome [1, 2, 5].

3. Pathophysiology

The pathophysiological mechanisms of JHS involve both genetic and environmental factors. Although several genes have been linked to the condition, their penetrance varies, and the influence of individual genes on the phenotypes is not well understood due to polygenic heterogeneity. Relevant polymorphisms have been identified in genes such as TNXB, COL3A1, and LZTS1, but further research is needed to clarify the role of genetic diversity in JHS [3].

Environmental factors such as weight gain, trauma, and surgical procedures also contribute to the development of unspecific articular hypermobility. These factors can lead to structural changes in joints, muscles, and connective tissue, resulting in chronic pain and altered proprioception [9]. The formation of micro-lesions in connective tissue may also facilitate joint fragility and structural damage, leading to a chain of events that culminates in chronic and debilitating pain [10].

The interaction between genetic predisposition and environmental factors gives rise to a wide range of JHS manifestations, which extend beyond musculoskeletal symptoms. A better understanding of the mechanisms underlying JHS is necessary to improve clinical management and potentially prevent the condition [11].

4. Diagnosis

Diagnosing JHS involves a thorough clinical evaluation. There are various connective tissue disorders that show general joint hypermobility, such as Marfan or Ehlers-Danlos syndromes (EDS). Since JHS is a diagnosis made by excluding other potential diseases, it is crucial to identify any other symptoms and carefully inquire about the family's medical history regarding connective tissue disorders. The symptoms of JHS and EDS-hypermobility type (EDS-HT) or type 3 are very similar. While other symptoms may aid in diagnosing non-EDS disorders, generalized joint hypermobility is usually the primary indicator of EDS. Table 1 provides a list of symptoms that can help differentiate between different disorders. [3, 5, 12, 13].

Table 1. *Differential diagnosis of joint hypermobility syndrome.*

DISEASE	CLINICAL FEATURES
Ehlers-Danlos syndrome (mainly type 3)	Stretchy, thin, soft, and velvety skin Positive family history Unexplained striae Generalized joint hypermobility Recurrent dislocations
Marfan syndrome	High stature Arachnodactyly Ectopia lens Aortic root dilation and aortic aneurysms Pectus excavatum
Osteogenesis imperfecta	Low stature Bluish sclerae Multiple fractures Sensorineural hearing loss Dental manifestations
Loeys-Dietz syndrome	Aortic aneurysms with dissection risk Hypertelorism Bifid uvula / Cleft palate

To standardize the assessment of generalized joint hypermobility, Beighton's score (Figure 1) was developed [14]. It consists of five simple maneuvers that measure the degree of hypermobility of each joint using a nine-point scoring system. A score of four or greater is considered indicative of generalized joint hypermobility [15], which is one of the major criteria for JHS according to Brighton's criteria (Table 2). The other major criterion is the presence of arthralgia in more than four joints that lasts longer than three months [16].

Additionally, a five-part questionnaire (Table 2) has been developed to screen for JHS [17]. A positive response to at least two of the five questions suggests a greater likelihood of joint hypermobility syndrome and warrants further

investigation. This tool is especially useful for primary care physicians due to its simplicity and objectivity [10, 17].

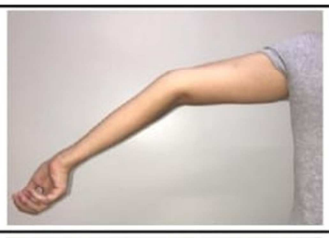
MANEUVER	EXAMPLE	NUMBER OF POINTS
Hyperextension of the elbows to more than 10 degrees		Each side made equals 1 point (maximum 2 points)
Hyperextension of the fifth finger		Each side made equals 1 point (maximum 2 points)
Hyperextension of the trunk with the palms of the hands touching the ground and with the knees extended		1 point if done
Knee hyperextension to more than 10 degrees		Each side made equals 1 point (maximum 2 points)
Juxtaposition of thumb and forearm		Each side made equals 1 point (maximum 2 points)

Figure 1. *The Beighton scoring system. Each of the above maneuvers earns 1 point, with a maximum possible score of 9 points. Scoring 4 or more points indicates the presence of generalized joint hypermobility.*

Table 2. *Brighton criteria for assessment of JHS and 5-Point Questionnaire for JHM.*

Brighton criteria for assessment of JHS		**5-Point Questionnaire for JHM**
MAJOR CRITERIA	CONSIDERATIONS	1) Can you now (or could you ever) place your hands flat on the floor without bending your knees?
Beighton score ≥ 4/9	Refer to Figure 1 for the calculation of the score.	
Arthralgias	For longer than 3 months, in more than 4 joints.	

Brighton criteria for assessment of JHS		5-Point Questionnaire for JHM
MINOR CRITERIA		2) Can you now (or could you ever) bend your thumb to touch your forearm?
Beighton score < 4	Score of 1, 2, 3 (<50 years) or 0, 1, 2, 3 (> 50 years).	3) As a child did you amuse your friends by contorting your body into strange shapes OR could you do the splits?
Arthralgias	1-3 joints, or back pain for more than 3 months, or spondylosis, spondylolysis, and/or spondylolisthesis.	4) As a child or teenager did your shoulder or kneecap dislocate on more than one occasion?
Dislocation or subluxation	In more than one joint or more than once in one joint.	5) Do you consider yourself double-jointed?
Soft tissue rheumatism	3 or more soft tissue lesions (e.g., epicondylitis, tenosynovitis, bursitis).	
Marfanoid habitus	Tall, thin build, arm span/height ratio > 1,03, lower limb length / upper body ratio <0,89, or arachnodactyly.	
Abnormal skin	Hyperextensible, thin, with striae or papyraceous scarring.	
Eye signs	Drooping eyelids or myopia or antimongoloid slant.	
Varicose veins or hernias or uterine/rectal prolapse		
Mitral valve prolapse		
DIAGNOSIS	Two major criteria or One major and two minor criteria or Four minor criteria or Two minor criteria and unequivocally affected first-degree relative in family history.	Affirmative answer for two or more questions.

5. Clinical Findings in Joint Hypermobility Syndrome

Patients with JHS can exhibit a wide spectrum of clinical manifestations [6]. Pain can have either a neuropathic (neurogenic) or a nociceptive (inflammatory) component. The former results from direct nerve fiber injury, while the latter is caused by the stimulation of peripheral pain receptors or local tissue damage. Nociplastic pain, observed in fibromyalgia and related conditions, may also be present due to hyperstimulation of nociceptive receptors by visceral or external factors. Chronic pain can affect any joint but is most commonly noticed in the knees and ankles. Since this symptom can worsen with poor exercise habits, patients often suspend all physical activity, facing the long-term downsides of sedentary behavior, including a worse prognosis and comorbidities [5, 9].

Impairment of the autonomic nervous system is frequent in JHS patients, significantly impacting their quality of life and mimicking several other conditions, making it even more challenging for physicians to reach an accurate diagnosis [18]. JHS patients experience significantly higher rates of autonomic nervous system-related symptoms, including syncope, presyncope, palpitations, chest discomfort, fatigue, and heat intolerance. The proposed pathophysiological mechanism underlying dysautonomia involves sympathetic nervous system dysregulation associated with α and β-adrenergic receptor hyperresponsiveness [19].

JHS has also been associated with gastrointestinal (GI) manifestations. Diarrhea, constipation, nausea, dyspepsia, and abdominal pain may be reported, with these symptoms being more frequent in older JHS patients. An association between JHS, dysautonomia, and GI symptoms has been proposed, but pathophysiological mechanisms remain unclear. Connective tissue involvement may be a trigger for GI symptoms [20, 21].

Patients with JHS also have a higher prevalence of anxiety, depression, and panic disorder, likely due to chronic symptoms such as long-lasting arthralgia and changes in sleep patterns [22-25]. Fatigue is also a frequent symptom experienced by individuals with JHS and significantly impairs their health-related quality of life. The diagnosis and management of chronic fatigue in these patients should include a comprehensive clinical examination and laboratory testing to exclude common causes of fatigue (e.g., hypothyroidism, inflammatory chronic diseases, anemia), as well as assessment of other factors such as sleep disorders, chronic pain, cardiovascular autonomic dysfunction, bowel and bladder dysfunction, psychological issues, and nutritional deficiencies [26, 27].

Neurological manifestations, including migraine, muscle tension headache, craniocervical instability, and temporomandibular joint disease, are common in patients with JHS. Females with JHS are particularly prone to frequent and disabling migraines [28-30].

Mitral valve prolapse (MVP) is included in the Brighton criteria for assessing JHS [16]. Physical examination may reveal the presence of a systolic click and a late systolic murmur heard best at the apex of the heart. Since other connective tissue diseases can also present with mitral valve prolapse, patients with suspected MVP and joint hypermobility syndrome should receive a cardiology consultation for further evaluation [5].

6. Treatment

JHS is a non-progressive and non-inflammatory condition, but it has a negative impact on productivity and quality of life due to debilitating and life-changing events such as recurrent joint dislocations, psychological trauma, long-lasting fatigue, and chronic pain [10]. Treatment for joint hypermobility syndrome requires a multidisciplinary approach involving patient education, self-care strategies, and pain management [31].

Physiotherapy has also been recommended as a treatment for JHS, as it has been shown to decrease pain, increase musculoskeletal resistance, and prevent joint injuries. It is

important to note that it is not established whether generalized exercises or specific group training work best for the condition [32, 33]. Regular exercise has been shown to provide relief from JHS symptoms. However, excessive joint movement, strenuous training, and excessive focus on articular flexibility may worsen symptoms and lead to injuries. Therefore, exercises that focus on balance and gentle stretching of joints may be more appropriate [34, 35].

Pharmacological measures such as oral analgesics, selective serotonin reuptake inhibitors, anticonvulsants, and tricyclic antidepressants may be helpful, but caution and short-term therapy are advised [36]. Primary healthcare physicians should be educated about the clinical presentation of the condition to facilitate timely diagnosis and management. Referral to a specialist is indicated in case of systemic symptoms, such as urinary dysfunction, gastrointestinal manifestations, and dysautonomia [10].

7. Conclusions

JHS is a prevalent condition that often presents as chronic pain and must be distinguished from other collagenopathies. Unfortunately, it is an underdiagnosed condition that carries a stigma due to a lack of awareness regarding its symptoms and prognosis. JHS can affect multiple systems beyond joints. Thus, physicians' awareness plays a crucial role in early disease detection, and continuing medical education should be promoted. A multidisciplinary approach that encompasses the integrality of care and patient education is essential when dealing with JHS. Therapeutics must be individualized and based on longitudinal monitoring, taking into account each patient's priorities. Lifestyle changes, physiotherapy, and physical exercise are the most important elements of care, while psychotherapy and self-care techniques are also supported. However, there is a lack of evidence regarding risk factors, prevalence, and specific interventions, indicating the need for further studies to assess the true impact of JHS and develop better practices.

Abbreviations

JHS: joint hypermobility syndrome
EDS: Ehlers-Danlos syndromes
GI: gastrointestinal
MVP: mitral valve prolapse

Author's Contributions

JLO conceived the article. Data acquisition, analysis and/or interpretation: SVPL, GST, RSCR, PIM, ABCC, PHSP, DJPA. Draft and revision of the work: IAN, CTN, JLO. All authors approved the final version of the manuscript.

Consent for Publication

Written informed consent was obtained from the patient to publish the image in this article. A copy of the written consent is available for review by the editor of this journal.

Competing Interests

The author declares that there are no competing interests.

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