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Joint hypermobility syndrome and related pain

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ABSTRACT

Hypermobility is defined as an abnormally increased range of motion of a joint resulting from the excessive laxity of the soft tissues. This paper is focused on this commonly forgotten cause of several morbidities. The etiology of hypermobility is not very well known. One decade ago, joint hypermobility syndrome was considered as a benign condition, but now it is recognized as a significant contributor to chronic musculoskeletal pain, besides impacting on other organs. Patients with joint hypermobility syndrome often have diffuse, chronic complaints that are inconsistent with the musculoskeletal system. Chronic pain may cause loss of proprioception and so increased sensitivity to microtrauma, premature osteoarthritis development, soft tissue problems, psychosocial disorders, and neurophysiological deficiencies. Osteoarthritis, pes planus, mechanical low back pain, and soft tissue rheumatisms are frequent musculoskeletal findings as well as subluxations, thoracic outlet syndrome, rectal and uterine prolapses, hernias, and stress incontinence. Joint hypermobility syndrome's treatment is not easy, and nonsteroidal anti-inflammatory drugs are not usually effective or adequate. Proprioceptive and strengthening exercises have been reported to have supportive and therapeutic effects, but we have limited data on this issue. Joint hypermobility syndrome must be accepted as a multisystem connective tissue disorder rather than just joint laxities. As a result; clinicians must be aware of complexities of connective tissue disorders and comorbidities.

Key words: *Hypermobility, benign joint laxity, chronic pain, joint instability, dysautonomia, Ehler-Danlos type III*

Introduction

Hypermobility is defined as an abnormally increased range of motion of a joint as a result of excessive laxity of the soft tissues. This paper draws attention over this commonly forgotten cause for many morbidities. Joint hypermobility syndrome must be accepted as a multisystem connective tissue disorder rather than just joint laxities. Attending physicians must be aware of complexities of connective tissue disorders and comorbidities.

Definition

The term "joint hypermobility syndrome" (JHS) was first introduced in 1967 [1]. The word 'benign' (BJHS) was added in 1996, when it was thought that life-threatening complications did not form a part of the clinical manifestations, unlike in the severe forms of congenital connective tissue diseases like Ehlers-Danlos syndrome, Marfan syndrome or osteogenesis imperfecta [2]. Joint hypermobility is caused by ligament laxity, whereas joint hypermobility syndrome

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(JHS) is a dominant genetically inherited disorder in which the genes coding collagen, elastin, fibrillin, and tenascin are on target. So current opinion depicts JHS as synonymous with type III Ehlers-Danlos syndrome [3]. Affected individuals express a defect in their type I and V collagen structure, and a probable tenascin-X deficiency. The variations or mutations of these genes may cause connective tissue disease and hypermobility of joints [4]. Patients who have laxities affecting their daily activities and symptoms threatening survival, may also have overlapping genetic connective tissue disorders like Marfan syndrome, Ehler-Danlos syndrome or osteogenesis imperfecta. But JHS is a more benign disorder that has no life-threatening complications. Joint hypermobility syndrome was found in 59.5% of panic disorder patients with mitral valve prolapse, in 42.9% of panic disorder patients without mitral valve prolapse and in 52.6% of control subjects [5]. Figure 1 depicts differential diagnosis (Figure 1).

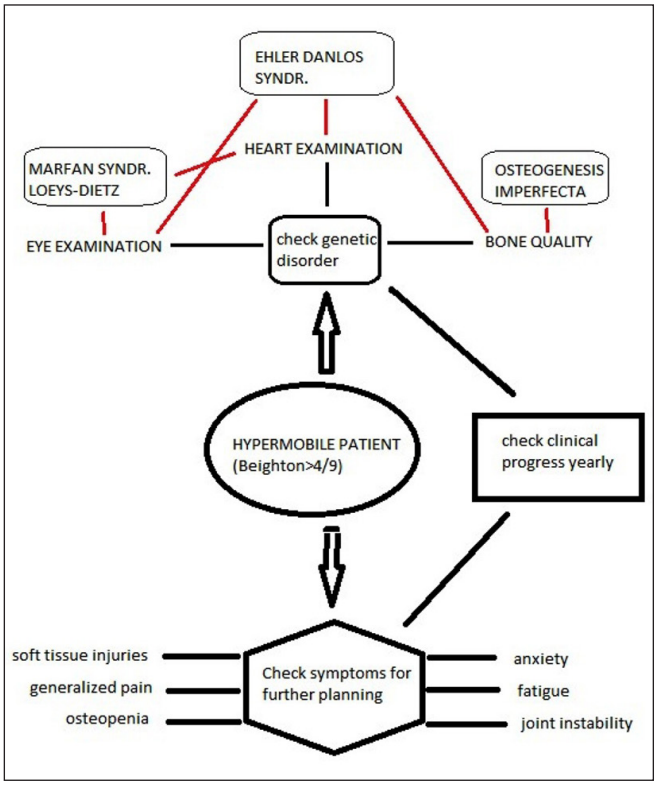

Figure 1. Differential diagnosis of a hypermobile patient.

Epidemiology

The epidemiological data for JHS is restricted and because the prevalence studies commonly include larger intervals, the exact prevalence is still in debate. Difficulties in diagnosing and lacking of uniform diagnosis criteria may cause problems in calculating prevalence [4]. Studies have shown that asymptomatic hypermobility is not rare and it should be differentiated from symptomatic JHS. Data have been published regarding age, sex or ethnicity [5,6]. It is more common in Asia, Africa, and Middle East [5,6]. The rates in prevalence studies include various rates like 43%, 0.6-31%, 2-5%. Female to male ratio is 5:1 [7]. JHS is more common among children than adults and decreases with age, which is why many studies have been carried on schoolchildren [5].

Etiology

When the pedigrees were searched, it was observed that JHS was a dominantly inherited genetic disorder. Although it was said that males and females of the same family were differently affected up to symptoms seriousness, placement and type, which could have been interpreted as an X-linked transmission or autosomal recessive trait, this situation was found to be free of X-linked trait or estrogen levels [8]. Furthermore, acquired polyarticular joint laxity can also be seen in some diseases like acromegalia, hyperparathyroidism, chronic alcoholism, systemic lupus erythematosus or in some occupations [8,9].

Pathology

A disruption in collagen type I and V is seen in JHS. Collagen type I has a big tension resistance and can be found in many connective tissues. Collagen type II is primarily found in cartilage, and type III localizes with type I but in lower amounts. In JHS the ratio of type III/type III+I increases, while this ratio is 18-21%, it is 28-46% in JHS [10]. Zweeres et al. showed that reduced tenascin-X serum levels were present in 5–10% of the patients diagnosed with BJHS or hypermobility type of Ehlers-Danlos syndrome [11].

In general, lesions affect the triple helix formation or cross-links of the collagen. Defects may be due to mutations that diminish or cease the synthesis of procollagen chains, production of shortened or lengthened procollagen chains, or insufficiency in processor enzymes [12].

Diagnosis

JHS is easy to diagnose if you are looking for it, but it is also very easy to miss if you are not. Diagnosis must be entirely done clinically because no current biological or imaging markers are available. A simple nine-

point scoring system was introduced by Beighton in an effort to increase the rates of diagnosis [13]. But its lack of sensitivity to patients' actual symptoms and lack of specificity to all joints, led to the development of the latest criteria by Brighton, in which 2 major, or 1 major and 2 minor, or 4 minor, or two minor criteria and a close relative, such as a parent, who has been diagnosed with joint hypermobility syndrome are enough for a diagnosis [14]. Any future improvement of the criteria must include etiological reasons in the subgroups, especially for osteoarthritis [6].

Minor Criteria

1. Beighton score: 1-2-3/9 (0, 1, 2 or 3 if age ≥ 50)
2. Arthralgia in 1-3 joints lasting at least for 3 months and more, or low back pain, spondylosis, spondylolysis/spondylolisthesis lasting for 3 months and more
3. Subluxation or dislocation in more than 1 joint or in one joint on more than one occasion
4. Soft tissue rheumatism with 3 or more involvement (epicondylitis, tenosynovitis, bursitis)
5. Marfanoid appearance (thin, slim, arachnodactyly, the ratio of upper: lower segment < 0.89, span/height ratio >1.03)
6. Abnormal skin (striae, hyper-extensibility, thin skin, papyraceous scarring)
7. Eye involvement (drooping eyelids or myopia or antimongoloid slant)
8. Varicose veins or hernias or uterine/rectal prolapse

Major Criteria

1. Beighton score ≥ 4/9 (either currently or in the past)
2. Arthralgia for longer than 3 months in 4 or more joints

Beighton's Nine-Point Scoring

- Ability to put hands flat on the floor when knees are straight (1 point)
- Ability to bend elbow backward (left 1 point, right 1 point)
- Ability to bend knee backward (left 1 point, right 1 point)
- Ability to bend thumb back on to the front of your forearm (left 1 point, right 1 point)
- Ability to bend little finger up at 90º (right angles) to the back of your hand (left 1 point, right 1 point)

Higher Beighton scores do not mean greater degrees of hypermobility, while a 4/9 score is enough to diagnose joint hypermobility, which can also be investigated with a simple questionnaire that was introduced by Hakim et al. that has a sensitivity rate of 84%, and a specificity rate of 80% [15]. The erythrocyte sedimentation rate, complete blood count, rheumatoid factor, antinuclear antibody, complements or serum immunoglobulin levels may all be within normal limits.

Musculoskeletal complaints commonly include: chronic widespread pain, fibromyalgia, joint and muscle aches which are worse at night, pain or fatigue after routine exercise, vulnerability to injury, poor fine-motor skills, anterior knee pain and patellofemoral instability, pes planus, non-specific low back pain, scoliosis, poor gait or running pattern, clicking of joints, orthostatic headache or locking/dislocating joints.

Pain

Interestingly, it has only been more than a decade since the relationship between JHS and chronic pain became apparent [16]. JHS patients mostly feel insidious, chronic and diffuse pain deriving from musculoskeletal impairment [15]. This pain may be accompanied by hyperalgesia or allodynia. Pain mostly begins in early stages and according to the 10-point scale, pain average is 4.3 and pain intensity is 5.3. Pain may be in the burning, sharp, pulsating or aching forms. Patients mostly complain about sleep disorders, school-job problems, decreased physical activity levels, or sexual problems together with pain. Hypermobility syndrome must be kept in mind for any patient with unexplainable musculoskeletal pain [16].

Studies among JHS patients revealed that these patients have a tendency to anxiety, depression, or anger [17]. Cole reported that 56% of hypermobile patients had treatments for depression or anxiety, 46% of patients used antidepressant or anxiolytic medications, and that many of them were misdiagnosed and mistreated for years [18].

The Reasons of Pain in JHS Can Be Explained in a Number of Ways:

1. *Connective tissue flexibility:* The increased levels of collagen type III in JHS patients eliminate the self-limiting and tenderness effect of soft tissue. Thus, overuse and tissue damage cause acute pain [6]. The

mechanism is thought to be that nociceptive input from over-stretched joints (especially in the lower extremity) aggravates the hypersensitivity to pain via central sensitization, in response to repeated harmful stimulation. This pain is generally resistant to pain-killers, and can be increased by any body movement [6].

2. *Psychosocial effects:* Tendency to traumas, painful soft tissue lesions and dislocations, and insufficient healing decrease pain threshold levels, and so depression, anxiety, panic disorder, agoraphobia and simple phobia may develop more easily. Kinesiophobia is the avoidance behavior from any pain-causing action, which can often be seen among JHS patients [19]. Psychosocial problems gather chronic pain. Bulbena et al. reported in their controlled study that major depression, anxiety, and dysthymic problems can be more common in JHS patients then in a healthy population [20]. Anxiety was seen in 67% of JHS patients, which is the highest percentage in rheumatological disorders, and a frequency 16 times higher than in the healthy population [21].

3. *Fibromyalgia:* Fibromyalgia syndrome (FMS) is characterized by sensitive points and diffuse pain. Hypermobility prevalence in FMS children was found to be 81% [10]. Hypermobile patients have more sensitive points inconsistent with the ACR criteria. Sleep disorders can affect 90% of JHS and FMS patients. Deficiencies in serotonin metabolism, level IV sleep pattern, increased levels of substance P, and insomnia may be the mutual reasons of psychological problems in both JHS and FMS patients [5,22-24]. Myofacial pain syndrome was also found in 81.7% of JHS patients [24].

4. *Fatigue:* Anxiety, fatigue, hypermobility, and diffuse pain may have a relationship depending on autonomic dysfunction. Hypermobility both causes anxiety-fatigue and chronic pain, which stimulate each other, and they cause autonomic dysfunction separately. It commonly plunges them into a rapid spiral of declining function, loss of independence, and self–efficacy [6].

5. *Osteoarthritis (OA):* JHS and patellar chondromalacia tend to be together [25]. Osteoarthritis [26] was found 34% of JHS patients. The main reasons for OA are a deficiency in proprioception and chronic microtraumas [10,27]. Premature OA is a common reason of pain in JHS [28,29].

6. *Neuropsychological factors:* There are three neurophysiological mechanisms causing pain:

a. Proprioception deficiency: Trauma is the most predisposing factor of pain [30]. And the most predisposing factor to trauma is deficiency in proprioception, which first happens in the knee and proximal interphalangeal joints of JHS patients. Unwanted ranges of motion can be prevented with proprioception, so it plays a protective role in traumas, and helps to coordinate complex locomotor movements [31]. Hall et al. found in their sex and age controlled study that the proprioceptive deficit was more common in JHS patients than in a normal population [32].

There are three subsystems responsible for joint stability:

- passive musculoskeletal system: bone, joints, ligaments, joint capsules, and muscles
- active musculoskeletal system: tendons and muscles around joints
- neural feedback mechanism: central and peripheral nervous system

The decrease in muscle tonus and tendon stressing affects these three subsystems [33]. Thus, proprioceptive deficit and abnormal motor control cause misalignment in mechanical axis and predisposition to OA [34]. This functional disability aggravates with the proprioceptive deficit due to muscle ligament injuries, slow gait speed, short gait, and decreased walking period [10]. Sahin et al. have reported that JHS patients have significantly impaired proprioception when compared to a healthy population. They concluded that proprioceptive exercises significantly decrease pain levels and improve functional status as well as occupational independency [35].

The neurodynamic function in JHS is affected by these connective tissue changes, which in the end cause immobility. This immobility increases with joint instability, muscle strength weakening, proprioceptive deficit, and frequent injuries [36].

b. Weakening in collagen fibers causes insufficient support, overstimulating the muscle and joint nociceptors and so culminating with pain [37]. In their 40-patient-study, Sahin et al. reported that the knee extensor muscle strength is significantly lower in JHS patients than in a healthy population due to the length-

ening of the quadriceps muscle, proprioception defect, and pain-associated inactivity [38].

c. For unknown reasons, JHS patients are resistant to topical or intradermal local anesthetics [39].

Visceral Symptoms in JHS

Pain is not the only consequence of the locomotor system problems. The inner organs are also affected directly with intrinsic weakening or indirectly with pleura, pelvic floor or anterior wall insufficiency. That is why uterine-rectal prolapses, abdominal hernias, and varicose veins are not rare. Spontaneous or minimally traumatized ecchymosis all around the body can be seen. Urinary incontinence rates are also higher [40,41]. Pelvic floor dysfunction is a frequent symptom, and both urinary and anal incontinence are statistically higher in women with JHS compared to control groups [42].

Gastrointestinal symptoms such as constipation, irritable bowel syndrome, gastro-oesophageal reflux and chronic abdominal pain have also been reported, [43] as well as higher rates of rectocoele, cystocoele or vaginal vault prolapse [44].

Autonomic dysfunction symptoms like palpitations, syncope, dizziness, chest discomfort, orthostatic hypotension and postural orthostatic tachycardia syndrome can be seen, especially in adolescent girls or in patients younger than 30 years old [45].

Treatment of Pain in JHS

Any treatment modality must have a multidisciplinary approach that involves health professionals like physiotherapists, occupational therapists, and podiatrists [46]. Psychiatry may be helpful to investigate psychosocial factors, and to help with pain management besides behavioral and cognitive behavioral therapies. Patient education, activity modification, stretching and strengthening exercises for the affected joint, and osteopathic manipulative treatments are all considerable for treatment.

Patients and their families must be sedated after the initial diagnosis and need to be educated about the diagnosis, determining which activities exacerbate their symptoms, so they can be allowed to make appropriate lifestyle modifications to keep their joints healthy. It is not a life-threatening occasion in general [30]. Appropriate pelvic floor physiotherapy is helpful perinatally, and also for assistance with incontinence and prolapse.

Analgesics and anti-inflammatory drugs have diminished effects on JHS patients. Pain-killers can be used in combination with opioids, antiepileptics, low-dose tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs), but frequently provide little benefit [6].

Recurrent, physically debilitating locomotor pain with visceral problems causes chronic diffuse pain, and secondary psychiatric problems. Despite pain-killers, pain causes emotional distress, and using unnecessary supportive splints may cause disabilities in the end [47]. A multidisciplinary treatment approach including cognitive therapy must be carried on. Every patient must be investigated and treated separately [48].

The aims of the treatment are: to decrease the pain and discomfort, to stop recurrences, to enhance physical activity, to diminish socio-economical load, and to heal psychosocial status. Patient's kinesiophobia decreases, and physical activity in daily life increases gradually. Thus, they can bear more responsibility as their functional capacity increases.

When loses its water, the connective tissue becomes less compliant and unstable with age, and this provides hope to JHS patients, who usually retain more stable joint ranges when getting older and can stay more active than their less agile counterparts in their elderly years.

Bale et al. reported no difference in clinical outcomes between structured multidisciplinary interventions and standard care protocols in their recent study [49]. But Bathen et al. showed significant changes in perceived performance of daily activities, a significant increase of muscle strength and endurance, and a significant reduction of kinesiophobia with a multidisciplinary approach and cognitive-behavioral therapy [50].

Conclusion

JHS must be accepted as a multisystem connective tissue disorder rather than just joint laxities. Precise diagnosis and appropriate management both physically and psychologically are essential factors for best results. Clinicians must be aware of the complexities of connective tissue disorders and comorbidities.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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