Joint Hypermobility Syndrome

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INTRODUCTION

Most rheumatologists have a basic appreciation of joint hypermobility (JH). They know that the term refers to the increased passive or active movement of a joint beyond its normal range. They are familiar with the 9-point Beighton score1 and many see this as the gold standard for recognizing JH. On an all-or-none basis, it signals the flexibility of 5 body areas (spine/hips and paired elbows, fifth metacarpophalangeals, thumb/wrists, and knees) as shown in Table 1, but takes no account of the rest. The maximum score is 9 out of 9. Higher scores do not represent greater degrees of JH, merely the number of joints affected out of a limited selection. A score of 4 or more out of 9 is arbitrarily considered to show the presence of generalized JH. However, it was introduced as an instrument for epidemiologic research; it was never intended to become a tool for clinical diagnosis. It is with the interpretation of hypermobility that most rheumatologists have difficulties. The wherewithal to establish a definitive diagnosis is lacking.

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differential diagnosis and thereby to develop an appropriate management plan is often lacking. This article is intended to assist colleagues in this critical task.

RECOGNIZING HYPERMOBILITY
The 5-Point Questionnaire

JH can also be identified reliably with the use of the 5-point questionnaire, which is a simple statistically validated questionnaire that accurately predicts the presence of hypermobility according to the individual’s response to 5 questions. It has an 84% sensitivity and an 80% specificity when 2 or more questions are answered in the affirmative (Box 1).2 This questionnaire is particularly useful as a screening tool when the person is not present or available for examination. It is easy and quick to complete, and therefore a useful research tool. It has been successfully used to estimate the heritability of hypermobility in a twin study.3

Hypermobility Syndrome

Hypermobility syndrome (HMS; later termed joint hypermobility syndrome [JHS]) is a poorly understood clinical entity, the nature of which has changed almost beyond recognition since it was first described by Kirk and colleagues4 in 1967. It was originally conceived as the occurrence of musculoskeletal symptoms in the presence of generalized joint hypermobility. These early workers in the field (being eminent rheumatologists) thought of it as a purely rheumatologic disorder that occurred in healthy individuals who happened (by chance) to be at the upper end of the spectrum of

Table 1
Nine-point Beighton hypermobility score

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<thead>
<tr>
<th>The Ability to:</th>
<th>Right</th>
<th>Left</th>
</tr>
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<tbody>
<tr>
<td>(1) Passively dorsiflex the fifth metacarpophalangeal joint to ≥90°</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>(2) Oppose the thumb to the volar aspect of the ipsilateral forearm</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>(3) Hyperextend the elbow to ≥10°</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>(4) Hyperextend the knee to ≥10°</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>(5) Place hands flat on the floor without bending the knees</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>9</td>
<td></td>
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</tbody>
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One point may be gained for each side for maneuvers 1 to 4 so that the hypermobility score has a maximum of 9 points if all are positive.

RECOGNIZING HYPERMOBILITY

The 5-Point Questionnaire

Box 1
Validated 5-point questionnaire for generalized JH

1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2. Can you now (or could you ever) bend your thumb to touch your forearm?
3. As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
4. As a child or teenager, did your kneecap or shoulder dislocate on more than 1 occasion?
5. Do you consider yourself ‘double-jointed’?

normal joint mobility. Although in their discussion they considered the alternative interpretation, namely that these individuals might have a heritable disorder of connective tissue (HDCT) akin to Ehlers-Danlos syndrome (EDS) or Marfan syndrome (MFS), they rejected it outright, without stating their reasons for doing so, carrying with them most of the rheumatologic community worldwide. It has taken nearly half a century to set the record straight. This realization arose from the steady acquisition by a handful of interested investigators of new knowledge that gradually accrued during the second half of the twentieth century. It started in the 1980s, with the observation that patients with JHS showed phenotypic overlap with patients with other HDCTs, notably with skin and skeletal manifestations, so that JHS began to seem more and more like EDS type III than a seemingly trivial rheumatologic disorder occurring in healthy people, as it was widely perceived. This change was swiftly followed by the revelation that gynecologic abnormalities arising from pelvic floor weakness, such as uterine prolapse, were frequently found among women with JHS. In the 1990s, the focus moved to the further revelations that chronic pain and dysautonomia were also becoming recognized as complications associated with JHS. It is only in the last decade that interest has focused on the gastrointestinal (GI) tract with the discovery of a strong association between JHS and functional disorders of the GI tract (functional GI disorders [FGID]).

Recognizing Hypermobility Syndrome: the Brighton Criteria for JHS

The Beighton score identifies JH but not the symptoms that may have arisen as a result of it. It could, therefore, never be used to diagnose JHS. Thus, before 2000, there was no reliable way of identifying the syndrome other than by using the 1967 definition, which was too inclusive to be of use for this purpose, and therefore research was hampered by the lack of any means of defining the phenotype or classifying the syndrome. The Brighton criteria were conceived in the 1990s and published in 2000 for the purpose of addressing this need. Like its predecessors, the Ghent criteria for MFS and the Villefranche criteria for EDS, the Brighton criteria comprise major and minor criteria and incorporated the Beighton score and, in addition, included the principal symptoms, notably joint/spinal pain, dislocations, soft tissue lesions, as well as overlap features of connective tissue disorder such as hernias, uterine/rectal prolapse, marfanoid features, and skin changes. The full criteria are shown in Box 2.

The diagnosis of JHS should always be considered against the background of the other HDCTs, and the clinician must be alert to the wider differential diagnosis, so that a working knowledge of the clinical features including prognosis and availability, or otherwise, of genetic testing of the other major HDCTs, such as MFS, EDS (other than type III), and osteogenesis imperfecta (OI) is important. There is currently no genetic test or other biological marker for EDS III or JHS. A recent guide to the diagnosis of HDCTs written from a rheumatologist’s perspective may assist readers in this task.

Epidemiology of JH and JHS

The epidemiology of JH and JHS are in their infancy. There are many published surveys of JH in different parts of the world among peoples of different ethnic origin, and it has long been recognized that the prevalence is highest among those of Asian origin, followed by those of African and then European origin. Strict comparisons have been hampered by the differing use of criteria and methodology.

It is now more than a decade since the Brighton criteria for JHS were introduced, but there have been no large epidemiology studies conducted to determine the prevalence of JHS using this (or any other) instrument.
In one district hospital–based study, it was observed that 45% of all attenders to a rheumatology clinic satisfied the Brighton criteria for JHS. This percentage was unexpectedly high, but similarly high prevalences have also been shown in a clinic with an interest in heritable disorders of connective tissue in Santiago, Chile, and in a population of 365 French undergraduate students (39.5%).

Systemic Complications of JHS

Many rheumatologists still harbor an outdated view that symptoms in JHS are confined to the musculoskeletal system and that noninflammatory joint, spinal, and soft tissue pain are a mechanical consequence of increased joint laxity, devoid of any systemic elements. This idea was the original concept in the 1960s when it was first described and in the decades that followed. However, despite mounting evidence to the contrary, showing that JHS is a systemic disorder, the concept proved difficult to shake, which explains why there is such confusion surrounding JHS today.

The multisystemic disorder incorporates 3 principal components: (1) chronic pain, (2) autonomic dysfunction, and (3) pan-GI dysmotility. These three aspects, either singly or in unison, emerge to become part of the natural history of the condition usually in the third decade, although it is increasingly recognized today in adolescents or even in younger children (Ninis N and Grahame R, unpublished data, 2013).

Chronic pain can either present as a significant intensification of preexisting joint and/or spinal pain or as a superadded layer of whole-body (or hemibody) pain that adds to the preexisting pain. Its advent may be triggered by unaccustomed physical exercise (like running a marathon), a road traffic accident or other traumatic event, or it may develop for no obvious reason. The distribution is nonanatomic. The pain is
Fig. 1. Differential diagnosis of a patient presenting with JH. (Data from Malfait F, Hakim AJ, De PA, et al. The genetic basis of the joint hypermobility syndromes. Rheumatology (Oxford) 2006;45(5):502–7; and Reproduced from Oxford University Press, with permission.)
usually resistant even to the most potent analgesics, including opiates. For this reason, pain management using cognitive behavior therapy (CBT) has become the treatment of choice. Chronic pain in JHS is often labeled fibromyalgia. Unless they are specifically sought, the features of JHS are overlooked and the true diagnosis missed.

Autonomic dysfunction is a frequently occurring feature of JHS. In one series it was identified (by the Brighton criteria) in 78% of patients with JHS compared with 21% of controls. The most common type of dysautonomia seen in JHS is postural tachycardia syndrome (PoTS), defined as an increase in heart rate of greater than or equal to 30 beats per minute on 60° head-up tilt table or on rising from the lying to the erect posture. Symptoms include palpitations, orthostatic intolerance (dizziness, presyncope, or syncope on standing), headache, impaired concentration, forgetfulness, irritability, fatigue, and heat intolerance.

**GI Manifestations**

The existence of JHS-related GI manifestations as distinct clinical entities is a recent discovery. The ramifications in terms of symptoms, altered physiology and morbidity, and treatment are currently being studied for the first time. As a consequence, few clinicians are yet aware of its occurrence or of the impact it can have on an affected patient’s quality of life. Because few readers are likely to have encountered this complication in their clinical practice, the remainder of this article concentrates on this aspect.

**Hypermobility and Abnormal GI Anatomy**

Hypermobility is associated with several anatomic abnormalities in both the upper and lower GI tract. In a study of 100 patients attending an endoscopy unit, the prevalence of JH in patients with hiatus hernias (22%) was significantly increased compared with age-matched and sex-matched controls without hernias (6%, \( P < .001 \)).

In patients with constipation and symptoms of rectal evacuatory dysfunction, those with JH had an increased prevalence of rectal morphologic anomalies compared with those without JH, most commonly large functional rectoceles (24%) and external compression of the anterior rectal wall (11%). Lower GI symptoms in JHS frequently overlap with urinary symptoms, and a urologic study of patients with lower urinary tract dysfunction similarly showed that patients with JHS were significantly more likely to have symptoms of rectal evacuatory dysfunction and evidence of rectal morphologic anomalies (eg, rectal prolapses) compared with those without JHS.

Case reports of patients with JHS describe further anatomic abnormalities in small numbers of patients, including diverticular disease and visceroptosis of the bowel. The latter is rare and refers to the downward displacement of abdominal organs below their natural position. It can cause kinking of blood vessels and nerves and thereby cause symptoms that can be severe. In one case, the patient presented with a 4-year history of abdominal distension and bloating that interfered with her eating and activities of daily living.

**Hypermobility and Abnormal GI Physiology**

There is a physiologic association between JH and constipation. In young boys, a higher prevalence of JH was shown in those with slow transit constipation compared with those without. Adults seem to have a different pattern of constipation and, in a study of patients referred for investigation of severe constipation, those with JH had a higher prevalence of rectal evacuatory dysfunction but not slow transit constipation,
with more severe constipation, greater abdominal pain, increased laxative use, and need for manual evacuation.\textsuperscript{25}

**Association Between JHS and GI Symptoms**

The association between JHS and GI symptoms was first described 8 years ago by Hakim and Grahame (Fig. 2).\textsuperscript{30} Patients with JHS attending a hypermobility clinic had significantly more GI symptoms compared with age-matched and sex-matched controls (37% vs 11%). The most common GI symptoms were nausea, abdominal pain, constipation, and diarrhea. It was thought that dysautonomia was one mechanism by which this may occur,\textsuperscript{7,30} and since then it has been shown that PoTS is associated with GI symptoms such as nausea, reflux, bloating, constipation, and diarrhea.\textsuperscript{11} Thus it seems that JHS, autonomic symptoms, and GI symptoms are linked, although the exact mechanism for the association is unknown.

Since that landmark study, other studies worldwide in specialist hospital settings have confirmed that GI symptoms are common in patients with an existing diagnosis of JHS. In a study of 21 patients with JHS attending a genetics clinic in Italy, 87% of patients had GI symptoms, most commonly dyspepsia (67%), gastroesophageal reflux (57%), recurrent abdominal pain (62%), alternating constipation and diarrhea (33%), and abdominal hernias (5%).\textsuperscript{31} Furthermore, the incidence of GI symptoms increased with age, and older patients with JHS were more likely to have GI symptoms than their younger counterparts.\textsuperscript{20}

Another study showed not only that GI symptoms such as constipation, diarrhea, bloating, and swallowing problems were associated with JHS but that these GI symptoms were also associated with clusters of other extra-articular symptoms, particularly cognitive problems, insomnia, postural dizziness, and syncope,\textsuperscript{31} which supported previous findings.\textsuperscript{29} Furthermore, there was large heterogeneity in presentation and with cluster analysis it was shown that 2 main clusters of symptoms, and therefore patients, were present. Musculoskeletal symptoms were prominent in both clusters but GI symptoms were particularly prominent in the group that also had high levels

![Fig. 2. Extra-articular symptoms in JHS. (Data from Hakim AJ, Grahame R. Non-musculoskeletal symptoms in joint hypermobility syndrome. Indirect evidence for autonomic dysfunction? Rheumatology (Oxford) 2004;43(9):1194–5; and Reproduced from Oxford University Press, with permission.)](image)
of fatigue, cutaneous changes, and orthostatic, immune, urogynecologic, visual, and respiratory problems.32

Thus the association between GI symptoms and JHS in specialist hospital settings seems to be consistent. Furthermore, there seems to be clustering of JHS and GI symptoms with several other symptoms, including musculoskeletal pain, fatigue, autonomic symptoms, and urologic symptoms, to varying degrees.

From a gastroenterology point of view, GI symptoms can be caused by organic disorders or FGID, the latter referring to disorders whereby symptoms arise in the absence of demonstrable changes on conventional testing (eg, irritable bowel syndrome [IBS]). There is literature, albeit limited, that associates JHS with both types of disorder.

JHS and Organic GI Disorders

Only 2 published studies exist that show a possible association between hypermobility and organic disorders. The first compared 69 patients with IBD with 67 age-matched and sex-matched controls. A significantly higher prevalence of JH was found in patients with Crohn’s disease (70%) compared with controls (25%) and with patients with ulcerative colitis (36%),33 suggesting a possible association between JH and Crohn’s disease, although this has not yet been replicated. In addition, only JH was assessed, so it is questionable whether the findings can be generalized to JHS.

The other study assessed 31 patients with JHS for celiac disease. Five (16%) had a confirmed diagnosis based on both serologic and histologic testing,34 which was significantly higher than the estimated population prevalence (1%). However, the patients were a highly selected group, attending specialist genetics clinics, and so may not represent most patients with JHS, most of whom remain undiagnosed and do not present to clinics.

Hypermobility and FGID

The only direct evidence for an association between FGID and hypermobility comes from a single retrospective observational study in the tertiary gastroenterology setting.11 In this study, the validated 5-point hypermobility questionnaire was used to screen for JH in 129 consecutive patients attending a neurogastroenterology clinic. The prevalence of JH in these patients was 49%, 3 times higher than the prevalence in healthy controls (17%). Those with JH were more likely to have GI symptoms without a known underlying structural, biochemical, metabolic, or autoimmune cause compared with those without JH (ie, the symptoms were more likely to be unexplained). A subgroup of these patients were assessed further by a rheumatologist and found to have JHS. These patients with JHS tended to have motility problems in their gut on physiologic testing, such as small bowel dysmotility, delayed gastric emptying, and delayed colonic transit. This study confirmed that, in a tertiary neurogastroenterology setting, JH was strongly associated with unexplained GI symptoms or FGID. It also showed that GI dysmotility is common in patients with GI symptoms and JHS, suggesting that these patients may have a neuromuscular basis for their symptoms. The cause of the dysmotility and the GI symptoms is as yet unknown but research is ongoing to determine whether this is a direct consequence of abnormal connective tissue in the gut, or of associated dysautonomia.

Although no large observational studies have been published that confirm an association between JHS and FGID, smaller studies have shown not only that IBS symptoms are common in JHS30,31,35 but that patients with JHS with GI symptoms often have a preexisting diagnosis of IBS.26,31
Further support for the association between JHS and FGID comes from both disorders sharing several features, in particular an association with several medically unexplained disorders, also known as functional somatic syndromes (Table 2). There is speculation that the same underlying process, involving a combination of somatic hypersensitivity, chronic pain, and dysautonomia, underlies all the functional somatic syndromes and that JHS is the common link (Fig. 3).36

Management of JHS

A full consideration of the treatment of JHS and related conditions is outside the scope of this article and can be found elsewhere.37,38 Physical therapies (in particular physiotherapy) has traditionally played the leading role in the rehabilitation of patients with JHS, although many patients question its benefit, whereas others attest to its counterproductive effects when inappropriately applied. It is only within the last couple of decades that pioneers in physiotherapy have studiously adapted the principles of physiotherapy to the needs of patients with lax and fragile tissues to good effect.39 The important discovery that joint proprioception is significantly impaired in JHS, and that its correction by physiotherapeutic means is beneficial in terms that go beyond the locomotor system, has laid the foundations of an evidence-based approach to management.40 As mentioned previously, the application of cognitive behavioral techniques to pain management plays an important role.

### Table 2

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<thead>
<tr>
<th>Similarities between JHS and FGID</th>
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<tr>
<td><strong>Demographics</strong></td>
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<td>Gender</td>
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<td>Age</td>
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<td><strong>Symptoms</strong></td>
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<td>Chronic pain</td>
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<td>Hypersensitivity</td>
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<td><strong>Diagnosis</strong></td>
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<tr>
<td><strong>Disease Associations</strong></td>
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<tr>
<td>Fibromyalgia^a</td>
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<tr>
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<td>Depression</td>
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<td>Temporomandibular joint disorder^a</td>
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<td>Pelvic/bladder pain^a</td>
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<td>Insomnia</td>
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<tr>
<td>Allergies/atopy</td>
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<td>Autonomic dysfunction</td>
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^a Functional somatic syndromes.
in enabling patients with secondary chronic pain to achieve an improved quality of life.\textsuperscript{21}

REFERENCES


\textsuperscript{428} Fikree et al


