A Prospective Evaluation of Undiagnosed Joint Hypermobility Syndrome in Patients With Gastrointestinal Symptoms

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BACKGROUND & AIMS: **The Joint Hypermobility Syndrome (JHS) is a common connective tissue disorder characterized by joint hyperflexibility, dysautonomia, and chronic pain. Gastrointestinal (GI) symptoms are reported in JHS patients attending rheumatology clinics, but the prevalence and symptom pattern of previously undiagnosed JHS in GI clinics are unknown.**

METHODS: **By using validated questionnaires, a prospective cross-sectional study in secondary care GI clinics estimated the prevalence of JHS in new consecutively referred patients, compared GI symptoms in patients with and without JHS, and by using multiple regression determined whether the burden of GI symptoms in JHS patients was dependent on chronic pain, autonomic, psychological, and medication related factors. A positive control group consisted of JHS patients referred from rheumatology clinics with GI symptoms (JHS-Rh).**

RESULTS: **From 552 patients recruited, 180 (33%) had JHS (JHS-G) and 372 did not (non-JHS-G). Forty-four JHS-Rh patients were included. JHS-G patients were more likely to be younger, female with poorer quality of life ($P = .02$) than non-JHS-G patients. After age and sex matching, heartburn (odds ratio [OR], 1.66; confidence interval [CI], 1.1–2.5; $P = .01$), water brash (OR, 2.02; CI, 1.3–3.1; $P = .001$), and postprandial fullness (OR, 1.74; CI, 1.2–2.6; $P = .006$) were more common in JHS-G vs non-JHS-G. Many upper and lower GI symptoms increased with increasing severity of JHS phenotype. Upper GI symptoms were dependent on autonomic and chronic pain factors.**

CONCLUSIONS: **JHS is common in GI clinics, with increased burden of upper GI and extraintestinal symptoms and poorer quality of life. Recognition of JHS will facilitate multidisciplinary management of GI and extra-GI manifestations.**

Keywords: Functional; Ehlers–Danlos Syndrome; Irritable Bowel Syndrome; Dyspepsia.

Gastrointestinal (GI) complaints are common in inflammatory connective tissue disorders such as scleroderma where symptoms such as dysphagia and reflux are associated with GI dysmotility.[1] Much less is known about GI involvement in noninflammatory hereditary connective tissue diseases, partly because they are rare. In contrast, joint hypermobility syndrome (JHS) is a common but underdiagnosed hereditary noninflammatory connective tissue disorder with a reported prevalence of around 20%.[2] The hallmark of JHS is joint hyperflexibility, referred to as generalized joint hypermobility, which is also a feature of other hereditary disorders of connective tissue such as Ehlers–Danlos syndromes (EDS). These are characterized by abnormalities in collagen synthesis and consist of 6 subtypes. EDS hypermobility type (EDS-HT), previously EDS III, is considered

Abbreviations used in this paper: **BDQ, bowel disease questionnaire; CI, confidence interval; COMPASS, Composite Autonomic Symptom Scale; EDS, Ehlers–Danlos syndrome; EDS-HT, Ehlers–Danlos syndrome hypermobility type; FGID, functional gastrointestinal disorder; GI, gastrointestinal; GSI, global severity index; IQR, interquartile range; JHS, joint hypermobility syndrome; JHS-G, previously undiagnosed joint hypermobility syndrome patients presenting to gastroenterology clinics; JHS-Rh, joint hypermobility syndrome patients referred from rheumatology clinics; non-JHS-G, patients without joint hypermobility syndrome presenting to gastroenterology clinics; OR, odds ratio; PoTS, postural orthostatic tachycardia syndrome; QOL, quality of life.**

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identical to JHS, and these terms are now used interchangeably.[3] Therefore, for the purpose of this article, the term *JHS* will also refer to EDS-HT.

Although a small proportion of patients with JHS have deficiency of tenascin-X, a glycoprotein regulating collagen deposition,[4] the majority of affected individuals have no known genetic or histologic basis for their symptoms, and so diagnosis is made clinically by using the 1998 Brighton criteria (Table 1).[5] This incorporates the many characteristics of patients with JHS and includes a measure of joint flexibility, the Beighton score.[6] As is evident from the Brighton criteria, JHS is a multisystem disorder with widespread, but mainly musculoskeletal, symptoms. During the past decade several additional clinical findings have been strongly associated with JHS, including autonomic dysfunction, normally manifesting as orthostatic intolerance and postural orthostatic tachycardia syndrome (PoTS), fibromyalgia, chronic pain, urinary problems, and anxiety disorders.[2,7–9]

GI symptoms have previously been reported in JHS,[10] but it was only in 2003 that an association between JHS and GI symptoms was documented.[8,11] In this study, 37% of JHS patients attending rheumatology clinics experienced GI symptoms, with increased nausea, abdominal pain, bloating, constipation, and diarrhea compared with non-JHS controls. A smaller study of 21 EDS-HT patients attending a genetics clinic demonstrated the presence of these symptoms and reflux in 86% of patients.[12] Although no systematic assessment of GI symptoms in JHS has been carried out in a GI setting, one study demonstrated the presence of generalized joint hypermobility in 49% of patients with functional gastrointestinal disorders (FGIDs) attending a tertiary neurogastroenterology clinic[13]; a proportion of these patients also satisfied criteria for JHS.

Table 1. 1998 Brighton Classification for JHS[5]

Major criteria
1. Beighton score of 4/9 or greater (either currently or historically)
2. Arthralgia for longer than 3 months in 4 or more joints

Minor criteria
1. Beighton score of 1, 2, or 3/9 (0, 1, 2, or 3 if aged 50+)
2. Arthralgia (for 3 months or longer) in 1–3 joints, back pain (for 3 months or longer), or spondylosis, spondylolysis, spondylolisthesis
3. Dislocation/subluxation in more than one joint or in one joint on more than one occasion
4. Soft tissue rheumatism: 3 or more lesions (eg, epicondylitis, tenosynovitis, bursitis)
5. Marfanoid habitus (tall, slim, span/height ratio >1.03 upper: lower segment ratio <0.89, arachnodactyly [positive Steinberg/wrist signs])
6. Abnormal skin: striae, hyperextensibility, thin skin, papyraceous scarring
7. Eye signs: drooping eyelids, myopia, or antimongoloid slant
8. Varicose veins, hernia, or uterine/rectal prolapse

NOTE. A diagnosis of JHS requires 2 major criteria, 1 major and 2 minor, 4 minor, or 2 minor in the presence of an unequivocally affected first-degree relative. JHS is excluded by the presence of Marfan syndrome or EDS (apart from EDS-HT).

From these studies it is evident that GI symptoms are present in 37%–86% of patients with an established diagnosis of JHS. Thus it would be expected that JHS patients would present to GI clinics, yet no studies have systematically investigated this. In addition, the generalizability of the above findings and relevance to general gastroenterologists are unclear for numerous reasons. All studies had taken place in tertiary settings where patients are not representative of the general JHS population[14] and are likely to manifest severe disease, resulting in an overestimation of GI symptom prevalence. Furthermore, the validity of the above studies is limited by small patient numbers,[12] differing assessments for JHS,[12,13] lack of validated tools for GI symptom assessment,[11,12] and lack of suitable control groups.[12] Last, none of the studies controlled for the presence of autonomic dysfunction, psychopathology, somatization, and chronic pain, all of which may be present in JHS[7,8] and might confound the observed relationship between JHS and GI symptoms.

Objectives and Hypotheses

Our aims were to determine (1) the prevalence and phenotypic severity of JHS in GI clinics; (2) whether in this setting, JHS is associated with a particular or excessive GI symptom burden and reduced quality of life (QOL) compared with patients without JHS; and (3) whether GI symptoms in JHS are interdependent with other patient characteristics previously associated with JHS (autonomic dysfunction, chronic pain, somatization, and psychopathology).

Methods

Study Design, Cohort Selection, and Setting

A prospective cross-sectional study design was used to address our aims.

The main study cohort was derived from consecutive new patients with GI symptoms (but without prior JHS diagnosis), aged 16–70 years, who were attending general gastroenterology clinics at a large university teaching hospital in London between April 2010 and April 2012. After hypermobility assessment, patients were categorized as JHS (JHS-G) or non-JHS (non-JHS-G). An additional smaller sample of consecutive new patients with GI symptoms and established JHS (diagnosed by rheumatologists after exclusion of other inflammatory connective tissue disorders) who were attending gastroenterology clinics during the same period formed a positive control group (JHS-Rh). This group was considered an exemplar group to help interpret directional differences observed in the main cohort between JHS and non-JHS subgroups.

All patients completed a set of validated questionnaires and were then assessed for JHS and fibromyalgia before seeing the attending gastroenterologist for their initial GI consultation. A double-blind design was used; patients