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Hypermobility Syndrome and Gastric Emptying Disorders



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Joint hypermobility syndrome (JHS) is a common hereditary non inflammatory connective tissue disorder associated with a variety of clinical presentations, including hypermobile joints that may be unilateral or bilateral, hyper extensible skin, easy bruising, frequent dislocations, poor wound healing, and abnormal scar formation. JHS continues to be misdiagnosed due to the wide range of symptoms and lack of specific testing for the various forms of the hereditary connective tissue disorder. While JHS has been primarily a rheumatological disorder, recent research and literature suggest that there is a strong correlation between JHS and Gastrointestinal disorders. The purpose of this review article is to evaluate the existing research and literature regarding the associations between JHS and gastroparesis. Our goal is to raise awareness of JHS as the reason behind chronic unexplained symptoms suggesting a gastric motility disorder as well as present the current standard tests used to identify suspected JHS cases.

INTRODUCTION

Surprisingly, hypermobility syndrome has been present throughout history dating as far back as 1250 B.C. Researchers explored the possibility of hypermobility syndrome portrayed in artifacts from Mesoamerica from 1250 B.C. to 900 B.C. The artifact is of a Tlatilco sculptural vessel in which an individual is portrayed lying ventrally with his feet positioned

flat on his head.¹ (Figure 1) From 1250 B.C. to 900 A.D. hypermobility has been identified at numerous historical relics of the Taíno civilization in the Greater Antilles at the Caribbean region, western and central Mexico, Guatemala, Cuba, Peru and Mayan cultures.¹ These artifacts depict distorted human images thought to represent either individuals who were well-trained or had the pathology of hyperextensibility of joints.¹

In a review of literature to include rheumatology in art, researchers found paintings dating back to 1638 that portrayed individuals with possible manifestations of hypermobile joints to include scoliosis, hyperlordosis, flat feet, hyperextended fingers, and Trendelenburg sign depicting a weakened hip joint.² The painting referenced here (Figure 2) is “The Three Graces” by Peter Paul

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Figure 1. “The Acrobat” Ceramic Art from Tlatilco Dated 1200 – 900 BCE

An individual is lying on the ventral surface with his feet positioned flat on his head.¹

Rubens in which the painting is thought to be of his second wife and her sisters (Figure 2). In the painting, all three women portray symptoms of hypermobility, which would support the theory that the painting in fact portrays benign familial hypermobility syndrome, which is thought to have a strong genetic component.^{2,3,4}

The first written description of hypermobility dates back to Hippocrates’ writings in “Airs, Waters and Places” in 400 BC in which he described the Nomads and Scythians having lax joints and scars in which he thought was due to attempts to scar and stiffen the joints by cauterization.^{5,6} The first comprehensive case report of hypermobility syndrome was described in 1892 by Dr. Tschernogobow at Moscow Venereology & Dermatology Society in which he described a 17 year old boy with hyperelasticity of the skin, hypermobility and laxity of joints.⁵ Edvard Lauritz Ehlers presented a case of a patient who had lax joints, hyperextensible skin and tendency of bruising with a history of delayed walking at the Dermatological Society of Denmark in 1899 combined with Henri-Alexandre Danlos’ report of a patient with vascular and inflammatory symptoms. This would come to be known as Ehlers-Danlos Syndrome as suggested by Frederick Parkes-Weber in 1936.⁵ In 1986 at a conference in Berlin, the foundation for diagnostic criteria for heritable connective tissue disorders (HCTDs) was developed.⁷

Types of Hypermobility Disorders

Joint hypermobility disorders are associated with three recognized inheritable disorders of connective tissue. There are three principle disorders that must be considered when a patient shows signs and symptoms of hypermobility to include 1) Marfan syndrome (MFS),



Figure 2. “The Three Graces” by Peter Paul Rubens (1577 – 1640)

Grace in the middle has scoliosis and a positive Trendelenburg sign. Grace on the left shows hyperextension of the finger and flat feet.²

2) Ehlers-Danlos syndrome (EDS) and 3) Benign joint hypermobility syndrome (BJHS). These primary disorders can have overlapping symptomatology, but there appears to be distinct features that set them apart including molecular biology and genetic abnormalities.⁴

JHS is considered by many experts in rheumatology to be indistinguishable from the most common variant of EDS, EDS hypermobility type EDS-HM. Joint hypermobility may be assessed using the Beighton score, which is a measure of generalized joint laxity or by using a validated 5 point screening questionnaire^{8,9} (Table 1. and Figure 3.), that highlight the questions to ask and physical exam findings in patients with the suspected diagnosis of hypermobility syndrome.

Prevalence of Hypermobility Syndrome

The prevalence of hypermobility syndrome varies depending on age, gender, and ethnicities.¹¹ The highest prevalence of hypermobility syndrome appears to be in children, women, and individuals of Asian, African, and Caucasian in descending order.¹² The estimated prevalence of diffuse hypermobility has been estimated to be between 10% to 35%.¹³ Women have a higher

Table 1. Five Point Questionnaire for Assessing Joint Hypermobility⁹

1. Could you ever place your hands flat on the floor without bending your knees?
2. 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 shoulder or kneecap dislocate on more than one occasion?
5. As a child or teenager did you consider yourself double-jointed?

Agreement: Affirmative answer for two or more questions⁹

incidence of hypermobility than men.¹² Prevalence of hypermobility syndrome is increased in the following clinical conditions:

- 64.8% in patients with fibromyalgia¹⁴
- 65.6% of children with arthralgia¹⁵
- 13.2% of patients screened in rheumatology clinics.¹⁶

According to Tinkle, recognition of joint hypermobility syndrome in the United States may be lower than other areas due to lack of training in recognition and management of the syndrome.¹⁷

Gastrointestinal Manifestations and JHS

Joint hypermobility syndrome is associated with a complex array of both physical findings as well as a manifestation of symptoms that may influence patient well-being. Although heretofore they were not being considered nor appreciated; one study found that among patients referred to a GI clinic by their primary care provider as many as 33% of patients had undiagnosed JHS¹⁸ which is considerably higher than the general population whose prevalence of JHS is thought to be 19.5% overall¹¹.

A case-control study conducted by Fikree and colleagues found that out of the 336 patients with functional gastrointestinal disorders (FGID), 39.0% were also diagnosed with JHS. FGID reported in this

analysis included epigastric pain syndrome, postprandial distress syndrome, functional dyspepsia, functional vomiting, chronic idiopathic nausea, and unspecified belching. The most notable association with JHS in this study was post prandial distress syndrome where 51.0% of FGID participants were diagnosed with JHD¹⁹. Another study conducted by Fikree evaluated 180 patients with JHS in which 41.4% reported postprandial fullness whereas only 27.1% of the non-JHS group presented with postprandial fullness with a calculated odds ratio of 1.74 (CI: 1.2-2.6, p=0.006)¹⁸

The Mayo clinic analysis of Ehlers-Danlos syndrome (EDS) related GI symptoms conducted by Nelson et al. found that 5.8% of all EDS patients suffer from increased postprandial fullness with a prevalence of 7.0% in Ehlers-Danlos syndrome- hypermobility type (EDS-HM) and classic EDS subtypes.²⁰ The difference in prevalence of nausea between EDS subtypes yielded no significant results.

Our purpose of this review article is to shine the light on JHS as one of the differential diagnosis in gastric motility disorders and related symptoms.

What is the Explanation for Impaired Gastric Emptying in JHS?

Postural orthostatic tachycardia syndrome (POTS) is an aggregate of symptoms caused by dysfunctional autonomic control mechanisms and is seen in many instances both in association with and outside of the setting of JHS. The diagnosis of POTS is made by an increase in heart rate of greater than 30 beats per minute within ten minutes of standing (or a head-up tilt) in the absence of hypertension with a resulting heart rate above 120 beats per minute.²¹ The clinical picture includes manifestations such as palpitations (92%), lightheadedness upon standing (87%), headaches (87%) and fatigue (90%).²² POTS may occur as an autoimmune phenomenon in conjunction with multiple autoimmune manifestations such as multiple sclerosis, Sjogren’s syndrome, systemic lupus erythematosus and raynaud’s phenomenon.²³ According to Benarroch POTS is also commonly found to be associated with insomnia and fibromyalgia.²¹

The relationship between POTS and EDS-HM was exemplified by an analysis of 35 patients conducted by De Wandele et al. They found that Quantitative Sudomotor Axon Reflex Testing (QSART) (an assessment of peripheral sympathetic nerve function)

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Figure 3. Methods of Determining JHM

Four of the five maneuvers are each done on the right and left sides and 1 point is given for each positive result. The highest possible score is 9. A Beighton score of ≥ 4 , out of a maximum of 9, is considered to be consistent with JHM.^{8,10}

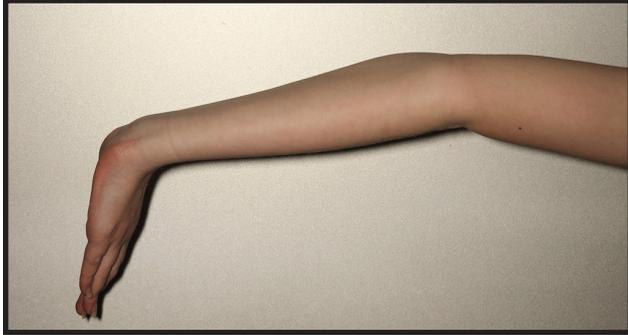


Figure 3a. 1 Point Each Side
Hyperextension of the elbow beyond 90° (neutral)



Figure 3b. 1 Point Each Side
Hyperextension of the knee beyond 90° (neutral)

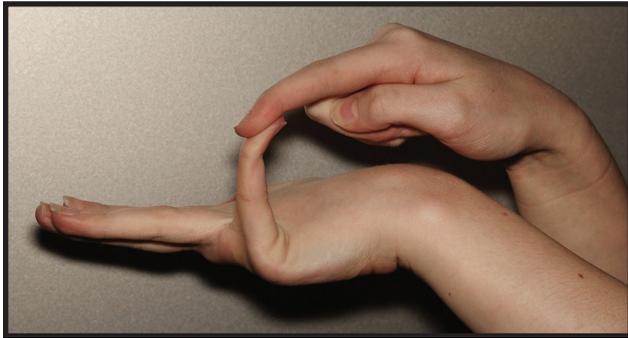


Figure 3c. 1 Point Each Side
Passive dorsiflexion of the metatarsophalangeal joint to 90°



Figure 3d. 1 Point Each Side
Apposition of the thumb to the flexor aspect of the forearm

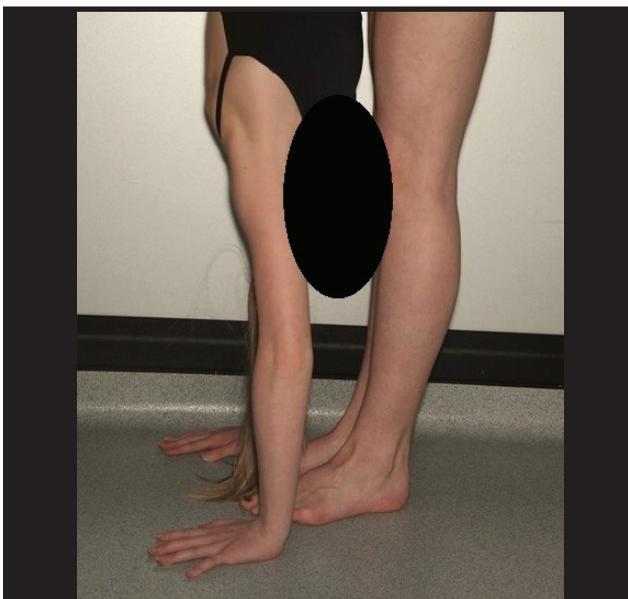


Figure 3e. 1 Point
Forward flexion with the hands flat on the floor and the knees extended

illustrated lower provoked sweat volumes at all sites and only 35% of the study population elicited a normal response.²⁴ Another study conducted by Zarate et al., found that six out of the 21 patients with BJHS demonstrated symptomatic evidence of autonomic dysfunction suggesting a higher prevalence of POTS in patients with co-existent JHS and FGID.²⁵

A large cohort study of 163 patients with POTS was evaluated and 55 (34%) were found to have a normal gastric emptying time, 30 (18%) had a delayed or slowed gastric emptying time, and 78 (48%) were found to have rapid gastric emptying.²⁶ This analysis by Loavenbruck illustrated that, while POTS is associated with delayed gastric emptying, the association with rapid gastric emptying is much greater.²⁶ However, whether delayed or accelerated it is clear that aberrations from normal emptying physiology are associated with POTS as 66% of the study population had abnormal gastric emptying times. The study also revealed the Tilt-test to induce elevations in heart rate more frequently in patients with

delayed gastric emptying. Delayed gastric emptying was associated with moderate to severe adrenergic dysfunction ($p=0.02$) as well as a greater increase in heart rate with deep breathing when compared to patients that fell within the normal gastric emptying time range ($p=0.02$).²⁶ The participants reported GI complaints that included nausea (21% of the study population), vomiting (10%), constipation (19%), and dyspepsia (18%). The only symptom found to be associated with a specific gastric emptying anomaly was vomiting. Another study conducted by Park et al. aimed at assessing the gastric emptying patterns in individuals with Postural Orthostatic Tachycardia Syndrome. 36 % of patients with POTS in this cohort had delayed (9 %) or rapid (27 %) gastric emptying.²⁷ In summary, two-thirds of patients with POTS and GI symptoms had abnormal gastric emptying. Rapid gastric emptying was the most frequently observed abnormality.^{26,27}

Gastroparesis may also occur in patients with joint hypermobility syndrome outside of the setting of postural orthostatic tachycardia syndrome. An interesting study published by Mayo clinic showed that abnormal gastric emptying was observed in 22.3% of EDS patients (17/76), 11.8% delayed and 10.5% accelerated²⁰. Another study by Zarate and his colleagues had shown delayed gastric emptying in patients with EDS.²⁵ Several mechanisms have been proposed to explain the etiology of abnormal gastric emptying and related symptoms in this patient population. A valuable consideration in the pathogenesis of dysmotility is the composition of the extracellular matrix in which the other components of the gut wall are embedded. The composition of the gut wall contributes directly to the mechanical properties of the gut wall including extensibility.²⁵ Alterations from physiologic norms in that regard are likely present with greater prevalence in patients with joint hypermobility syndrome leading to the association with gastroparesis. Zarate et al. further explains that changes in the degree of the stretch capacity of the gut wall influence the functional capacity of mechano-receptors altering the receptive signals that facilitate gastric emptying.²⁵

From review of the literatures, it seems that rapid gastric emptying is more common than delayed

emptying in the settings of POTS with JHS. However in the case of JHS without POTS gastroparesis or rapid emptying seems to occur in approximately equal proportions. These findings need to be confirmed and further evaluated in a larger cohort of patients with JHS.

CONCLUSION

JHS is considered a common disorder associated with multiple signs and symptoms included but not limited to hypermobility of joints, skin hyper extensibility, easy bruising, and many others. For years JHS was considered mainly a joint disorder with less focus on other systemic manifestation such as GI. Studies have confirmed the association between JHS and gastric abnormalities, also concluding that abnormal gastric emptying can be associated with or without accompanying POTS. GI practitioners should consider JHS as one of the differential diagnoses for idiopathic gastroparesis or nausea and vomiting of unknown etiology. In patients presenting with GI signs and symptoms, JHS can be recognized if practitioners are familiar with its manifestations. Gastroenterologists should definitely incorporate into their office exam a new repertoire focusing on hand and joint flexibility; particularly patients' ability to place the palms flat on the ground without knee bending, hyperextensin of elbows and or knees beyond 90 degree. Hypermobility joint syndrome has definitely arrived as a new under-recognized condition which contributes to the spectrum of idiopathic gastric motility disorders. ■

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