Is there a relationship between joint hypermobility and gastrointestinal disorders in children?

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ABSTRACT

Background. The main aim of the study was to assess the association between joint hypermobility (JH) and gastrointestinal (GI) disorders in children.

Methods. All children aged 4-17 years attending the clinics of the participating Pediatric Gastroenterology Centres for functional GI disorders (FGIDs) and inflammatory bowel disease (IBD) were screened for joint laxity. JH diagnosis was inferred using the Beighton Score. JHS diagnosis was inferred based on the Brighton Criteria. Rome III Diagnostic Criteria were used to diagnose possible FGIDs. Ulcerative colitis and Crohn's disease diagnoses were made according to the Porto Criteria. Age and sex- matched healthy children were enrolled as controls.

Results. One-hundred-seventy children with GI disorders (70 with FGIDs, 50 with Crohn's disease, and 50 with ulcerative colitis) and 100 healthy controls were enrolled in the study. JH was reported in 7/70 (10%) children with FGIDs (p=0.26 compared to controls), 4/50 (8%) children with Crohn's disease (p=0.21 compared to controls) and 15/50 (30%) children with ulcerative colitis (p=0.09 compared to controls; p=0.01 compared to FGIDs; p=0.01 compared to Crohn's).

Conclusions. JH is more prevalent in patients suffering from ulcerative colitis compared to the healthy general population, yet the difference did not reach statistical significance. Likely, a proportion of children with ulcerative colitis and JH may show connective tissue abnormalities. However, whether JH can be considered a possible feature of pediatric GI disorders deserves further investigation.

Key words: joint hypermobility, joint hypermobility syndrome, inflammatory bowel disease, ulcerative colitis, children.

Joint hypermobility syndrome (JHS) is the most prevalent of the hereditary disorders of connective tissue characterized by joint hypermobility (JH), the others being Marfan syndrome, Ehlers–Danlos syndrome, and *osteogenesis imperfecta*. JHS is defined as "musculoskeletal symptoms in a hypermobile individual in the absence of systemic rheumatological disease" and its prevalence is around 0.5% of the population.[1] JH, besides being a common clinical feature of the hereditary disorders of connective tissue, is also a common phenomenon in the healthy general population and represents one extreme of the physiological range of joints laxity.[2]

It has been recently pointed out that most of the features of JHS, such as symptom-based diagnosis in the absence of validated biomarkers, youth

and female gender prevalence, and association with other diseases like fibromyalgia, migraine and sleep disturbance, are common features in most functional gastro-intestinal disorders (FGIDs).[3] FGIDs include a combination of chronic or recurrent gastrointestinal age-dependent symptoms not explained by known biochemical or structural abnormalities.[4] They represent a challenging group of conditions that are frequently misdiagnosed in children and are associated with significant morbidity and high health care costs, accounting for more than 50% of the consultations in pediatric gastroenterology practice and from 2 to 4% of all general pediatric office visits.[5] Over the last years, interest in the study and recognition of FGIDs in children has escalated. Despite some promising developments, more research is needed to further advance the science underlying the pathophysiology and treatment of these conditions, which remain one of the unmet needs in the modern pediatric gastroenterological practice.

Aside from FGIDs, over the last years a few reports have shown an association between JH/JHS and organic diseases as well, such as Crohn's disease and celiac disease, thus raising the hypothesis that collagen varieties may play a role in their pathogenesis.[6,7] Evidence in pediatric age is still very limited.

The primary aim of our study was to assess the relationship between JH and both functional and organic GI disorders in a pediatric population. The secondary objective was to identify a possible subgroup of children with GI disorders who are more likely to suffer from JH.

Material and Methods

All consecutive children and adolescents aged between 4 and 17 years attending the clinics of the participating Pediatric Gastroenterology Centres for FGIDs and inflammatory bowel disease (IBD) from November 2014 to May 2015 were eligible for the study. All patients were screened for JH by one of the study investigators, using the 9-point Beighton score as described in Table I. JH diagnosis was assumed as having a Beighton score higher than 4.[8] A proportion of patients who were found to have JH was referred to a tertiary referral clinic run by a rheumatologist for further evaluation. JHS diagnoses were inferred only by the rheumatologists based on the Brighton criteria.[9] Quality of life of all the enrolled children was scored by the use of a validated questionnaire.[10,11]

The GI diagnostic evaluation included pH-impedance, gastric emptying, bowel transit time, manometric or endoscopic evaluation, and blood and fecal laboratory tests (complete blood count, inflammatory markers, anti-transglutaminase and anti-endomysial antibodies, fecal calprotectin), according to children's clinical picture and to the pediatric gastroenterolgist's free judgement. Rome III diagnostic criteria were used to diagnose possible FGIDs. Ulcerative colitis and Crohn's disease diagnoses were made according to the Porto Criteria.[12]

After a functional or organic diagnosis was confirmed, patients with JH were compared in terms of clinical characteristics to those without JH. Patients who had a diagnostic reassessment

Table I. Nine-point Beighton hypermobility score.

Maneuvers	Score
Passive dorsiflexion of fifth metacarpophalangeal joint to ≥90°	1 point each for left and right
Opposition of thumb to volar aspect of ipsilateral forearm	1 point each for left and right
Hyperextension of elbow to ≥10°	1 point each for left and right
Hyperextension of knee to ≥10°	1 point each for left and right
Place hands flat on floor without bending knees	1 point

A score >4 out of 9 is consistent with joint hypermobility.

or whose diagnosis had been questioned during the study period were excluded from the study.

Age and sex-matched healthy children were enrolled as negative control group among brothers or sisters of children attending the clinics or from children attending the clinics for well-child routine visits, and were screened for both JH and JHS, once the presence of any GI disorder was excluded.

Statistical analysis

Study data were entered into Excel (Microsoft, Redmond, WA) and analyzed with GraphPad PRISM software, version 5.01. Results are expressed as mean ± standard error and percentages. Statistical analyses include Student's t-test, chi-square test, and Fisher's exact test, with significance accepted at the 5% level. The sample size was computed considering an expected difference in the studied variable between the 2 groups of approximately 15-20% (power 80%; confidence interval 95%; first type error 0.05).

The study was approved by the Independent Ethics Committee of the University of Naples Medical School (rep. num. 0187/2015) and was conducted in accordance with the Declaration of Helsinki and Guidelines for Good Clinical Practice. An informed consent was obtained at enrolment from parents of all children younger than 10 years, and from both parents and children, if older than 10 years.

Results

One-hundred and eighty-six children and their parents agreed to participate and were enrolled in the study. Of these, only 170 (89 boys; mean age 120.6 ± 51 months; age range: 49-204 months) were included in the analysis since 16 had a diagnostic reassessment during the study period or, alternatively, were lost to follow-up. One-hundred age- and sex-matched healthy children were recruited as the control group (55 boys; mean age 123.5 ± 44 months; age range: 58-199 months).

Twenty-six out of 170 (15.3%) patients of the study group and 17 out of 100 (17.0%) children of the control group had clinical evidence of JH according to the Beighton score (p=0.73). Among the study group, only 1/170 (0.6%) also fulfilled the Brighton criteria and was therefore diagnosed as having JHS while no healthy children met the criteria for JHS (data too small to be analyzed). Compared to those without evidence of JH, children with JH had a similar age (133.3 months vs. 133.5 months, respectively) and were more frequently female (54.3% vs. 45.7%, respectively; p = 0.72 in the study group whereas were older (135.9 months vs. 105.5 months, respectively; p = 0.44) and more frequently female as well (66.7% vs. 33.3%, respectively; p = 0.18) in the control group.

Among the study group, 70 children fulfilled the criteria for FGIDs, mainly functional constipation (FC; n=32) and irritable bowel syndrome (IBS; n=19) and 100 suffered from IBD, 50 of which from ulcerative colitis and 50 from Crohn's disease. JH was reported in 7/70 (10%) children with FGIDs (p=0.26, compared to controls), 4/50 (8%) in children with Crohn's disease (p=0.21, compared to controls) and 15/50 (30%) in children with ulcerative colitis (p=0.09, compared to controls; p=0.01, compared to FGIDs; p=0.01 compared to Crohn's). Figure 1 summarizes the prevalence of JH among children with different GI diagnoses compared to controls.

The mean score of the quality of life was 97.0/100 among the control group, 88.4/100 among patients with FGIDs, 91.4/100 among patients with Crohn's disease, and 92.1/100 among patients with ulcerative colitis. Children with JH had a mean quality of life score of 96.4/100, whereas children without JH had a mean score of 94.3/100 (no statistically significant difference detected).

Discussion

This study evaluated the association between JH and both functional and organic GI
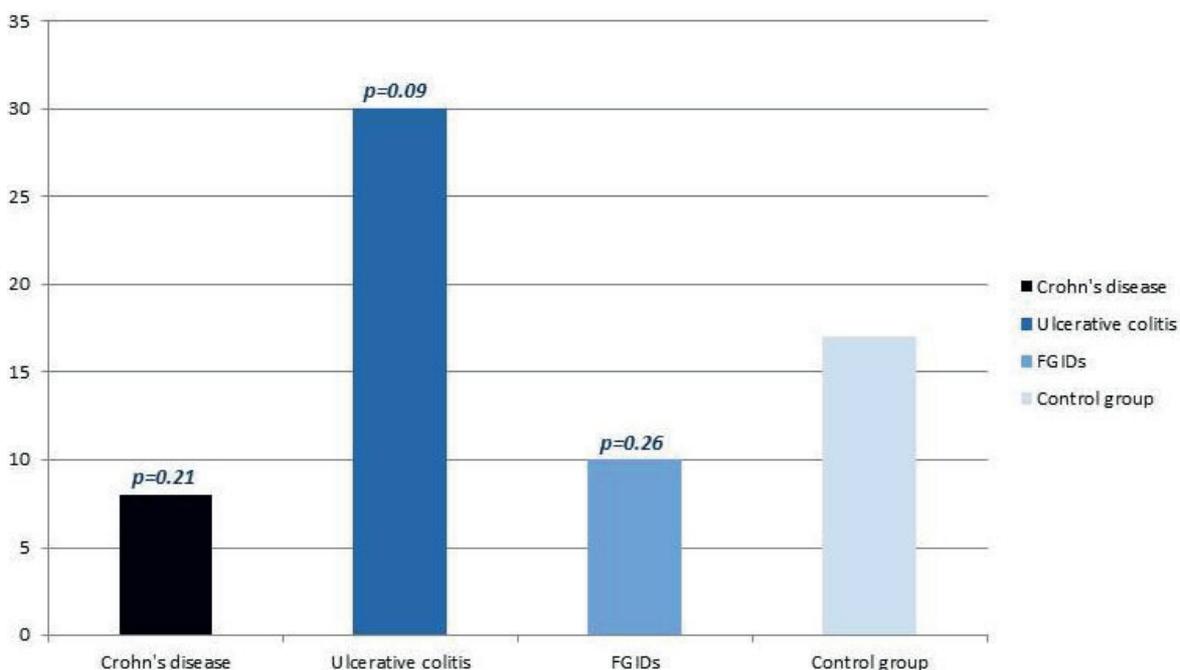
p values are computed in comparison with the control group

Fig. 1. Prevalence (%) of joint hypermobility in children with Crohn's disease, ulcerative colitis, functional gastro-intestinal disorders (FGIDs) vs. control group.

disorders in a cohort of pediatric patients attending a tertiary care gastroenterology unit. JH was more prevalent in patients suffering from ulcerative colitis compared to the healthy general population, although the difference did not reach statistical significance. Conversely, children suffering from other GI disorders, such as Crohn's disease and FGIDs, showed a lower rate of JH. When compared to these two groups of patients, the rate of JH in children with ulcerative colitis reached statistical significance.

The association between JH and GI symptoms in adults was first described 10 years ago by Hakim and Grahame.[13] Since that landmark study, other studies in specialist hospital settings worldwide have confirmed that GI symptoms are common in patients with an existing diagnosis of JH.[14-16] Direct evidence for an association between FGIDs and hypermobility comes from a single retrospective observational study in an adult tertiary gastroenterology setting.[3] The Authors of this study used the

validated 5-point hypermobility questionnaire to screen 129 consecutive patients attending a neurogastroenterology clinic. The prevalence of JH in these patients was 49%, about 3 times higher than the prevalence in healthy controls (17%). Subjects with JH were more likely to have GI symptoms without a known underlying structural, biochemical, metabolic, or autoimmune cause compared to those without JH. A subgroup of these patients was further assessed by a rheumatologist and was found to have JHS. These patients suffering from 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. Furthermore, it 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. A few years later Zweig et al.[17]

provided further evidence about the possible link between JH and FGIDs, collecting data from a population of IBS patients. Their main finding was the significantly higher prevalence of JH in patients with constipation predominant IBS compared to patients with diarrhea predominant IBS.

In recent years, two studies published by an Italian and a Greek study group highlighted a possible association between hypermobility and GI organic disorders, such as Crohn's disease and Celiac disease, as well.[6,7] Finally, Fikree et al.[18] reported that, compared to patients without hypermobility, those with JH, experience more reflux and dyspepsia, and also more commonly complain from chronic pain, fibromyalgia, and autonomic symptoms.

In 2015, Castori et al.[19] reviewed all the available evidence and confirmed a strong relationship between a variety of GI disorders and JHS.[19] According to the authors' opinion, given the relatively high frequency of this condition compared to other heritable connective tissue disorders, JHS emerges as a model for studying the pathophysiologic basis of such an association and, reasonably, identifying more tailored management and treatment approaches. Moreover, these studies emphasize the relevance of raising the scientific interest in this field. Indeed, accumulated evidence on the non-casual association between JH and many potentially disabling GI disorders opens a novel approach for interpreting highly prevalent complaints in humans.

Evidence in pediatric age is still very limited. A 2008 study by an Australian group showed a higher prevalence of JH in young boys with slow transit constipation compared with those without constipation, suggesting a possible relationship between the two conditions.[20] More recently, Kovacic et al.[21] analyzed a cohort of children with FGIDs, showing a high prevalence of both JH and comorbid symptoms, including sleep disturbances, chronic fatigue, migraine headache, dizziness, chronic nausea,

and fibromyalgia, that markedly affected the subjects' social life.

The main findings of the present study are partially in disagreement with the results of the aforementioned studies, since we found an increased rate of JH only in children with ulcerative colitis, whereas we reported a lower prevalence in children with Crohn's disease and FGIDs. However, the rate of JH that we found among healthy children is quite comparable to that reported in previous studies.[20-22] Likewise, the higher prevalence of JH in females has already been reported.[21] The frequent objective evidence of JH in many children with ulcerative colitis leads to the intriguing hypothesis of a new possible contributing etiologic factor. How could connective tissue defects be related to a chronic inflammatory condition is still to be determined. Perhaps alterations in the integrity and mechanical properties of the intestinal wall and distensibility of the gut may lead to altered motility and pain perception. Nevertheless, the biochemical mechanisms underlying these GI symptoms remain to be studied.

The prevalence of JH in our FGIDs and Crohn's disease study groups is comparable to that reported in healthy children. This finding contradicts the results of the aforementioned studies that reported a higher prevalence in adults and children with these disorders. Since the diagnostic tools and the sample sizes are similar among the different studies, we are not able to provide any possible explanation about the controversial results.

Finally, the evaluation of the quality of life in all the enrolled patients showed no difference between patients with and without JH. Furthermore, it allows an intriguing analysis of the impact of the different GI disorders. As already reported by recent papers, children's social and mental health was not affected by the functional or organic nature of the diagnosis, being slightly lower in children with FGIDs than IBD.[23,24]

Our study has possible shortcomings. Although it is acknowledged that anxiety and social stressors play key roles in both functional and organic disorders, the study lacks an accurate evaluation of these factors, limiting study interpretation and particularly the role of behavioral symptom amplification. Future prospective studies should include validated, psychosocial measures, such as an anxiety/depression evaluation. Moreover, our tertiary care cohort likely suffers from a referral bias with higher symptom severity and complexity than a community population with GI disorders, thus limiting our findings. Finally, even if the overall sample size of the present study is adequately large, it would lack power if we wanted to analyze patients with different FGIDs, such as IBS and FC.

On the other hand, our study shows several strengths. The objective nature of the hypermobility assessment, performed by the same physician per Centre for all the patients, rules out any possible bias related to different unreliable interpretations. Moreover, the physician who performed the joint laxity assessment was usually unaware of the diagnosis thus avoiding another major bias. Since JH has been reported to vary widely according to both age and gender, the present study included an age- and sex- matched control group, which allowed a relevant comparison, an essential feature conferring a clinically relevant meaning to connective tissue abnormalities in GI diseases.

In conclusion, our study shows that the prevalence of JH among children with FGIDs and Crohn's disease is comparable to that reported in healthy children, whereas children with ulcerative colitis were shown to have a higher prevalence of JH, although not reaching statistical significance vs. healthy children. Although preliminary, our data concur in making a step forward in a new and promising area of research. The existence of a possible overlap between JH and ulcerative colitis

suggests that the two conditions may share a common pathophysiology with collagen tissue changes exerting a contributory role. New, larger studies could help explain this relationship, providing a better understanding of the possible role of abnormal connective tissue in the GI tract.

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