RESEARCH LETTER

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Screening for Celiac Disease in the Joint Hypermobility Syndrome/Ehlers–Danlos Syndrome Hypermobility Type

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TO THE EDITOR:

Joint hypermobility syndrome (JHS) is a relatively common, but largely unrecognized heritable connective tissue disorder mainly characterized by joint hypermobility (JHM) and related musculoskeletal and non-musculoskeletal features [Grahame, 2010]. A recent consensus statement defines JHS as indistinguishable from the Ehlers–Danlos syndrome hypermobility type (EDS-HT), which now can be considered one and the same with the former [Tinkle et al., 2009]. The associated clinical spectrum of JHS/EDS-HT is wide and a growing number of studies highlight the overlap with various functional somatic syndromes, including fibromyalgia [Acasuso-Díaz and Collantes-Estévez, 1998], chronic fatigue syndrome [Castori et al., 2011], dysautonomia [Gazit et al., 2003], and functional gastrointestinal disorder [Zarate et al., 2010]. In particular, unexplained gastrointestinal symptoms, including recurrent abdominal pain, bloating, nausea, reflux, vomiting, constipation, and diarrhea, are found in 35–86% of JHS/EDS-HT patients [Hakim and Grahame, 2004; Castori et al., 2010; Zarate et al., 2010]. Conversely, JHS and/or generalized JHM are found to be more common among patients suffering from chronic (slow transit) constipation [de Kort et al., 2003; Manning et al., 2003; Reilly et al., 2008], hiatus hernia [Al-Rawi et al., 2004], Crohn's disease [Vounotrypidis et al., 2009], fecal incontinence [Arunkalaivanan et al., 2009], rectal evacuatory dysfunction [Mohammed et al., 2010], and functional gastrointestinal disorder [Zarate et al., 2010].

Coeliac disease (CD) is a gluten-sensitive condition with an estimated prevalence close to 1% in Western European populations [Dubé et al., 2005]. A diet of gluten in CD patients causes a wide variety of systemic consequences including, for example, chronic fatigue, bloating, constipation, diarrhea, abdominal pain, and osteopenia/porosis. All these features are equally common in JHS/EDS-HT subjects. Although expert opinion does not suggest an increased rate of CD in JHS/EDS-HT [Tinkle, 2010], no systematic study has yet been done on this point.

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From a total of approx. 100 index patients with various forms of EDS, we selected 31 individuals with a firm diagnosis of JHS and/or EDS-HT, who were available for further studies aimed at investigating their gastrointestinal complaints. Diagnosis was based on published diagnostic criteria including the Brighton criteria for JHS [Grahame et al., 2000] and the Villefranche criteria for EDS-HT [Beighton et al., 1998]. Patients were included if met at least either one of these two sets. In our clinical practice, the Brighton criteria are the most stringent for young-adult, adult, and elder patients, while the Villefranche criteria are the best for individual in the pediatric age. For this study, JHM was mainly assessed applying the BS [Beighton et al., 1973] and no further joint or group of joints other than those comprised in this score was registered. Skin/superficial connective tissue features were assessed qualitatively on the basis of accumulated experience. Other heritable connective tissue disorders were excluded clinically. Individuals with a doubtful or incomplete diagnosis were excluded. This implied that a group of patients with features of JHS/EDS-HT still insufficient for

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a firm clinical diagnosis based on available diagnostic criteria, but likely destined to develop full-blown JHS/EDS-HT were not included.

Twenty-five patients were females and 6 males with an age at diagnosis ranging from 10 to 54 years. Main clinical features of the patients' population were summarized in Table I. The BS ranged from 0 to 9 (mean = 5.16). Twenty-four patients showed a BS ≥ 5 and met the diagnostic criteria for EDS-HT, while 8 additional patients with a more limited joint motion met the Brighton criteria for JHS. All patients underwent determination of the plasma levels of specific auto-antibodies (Ab), including IgA and IgG antigliadin Ab (AGA), IgA and IgG antiendomisium Ab (EMA), and IgA and IgG anti-tissue transglutaminase Ab (anti-tTG).

Six (6/31; 19.3%) subjects resulted positive to the screening for IgA/G EMA and or anti-tTG and were asked for jejunal biopsy. Five of them (5/31; 16.1%) accepted, and histologic examination revealed chronic inflammatory infiltrate and the typical villous atrophy in all, according to the Marsh classification [Oberhuber, 2000]. JHS/EDS-HT patients with confirmed or suspected CD were instructed for a gluten-free diet and all showed amelioration of symptoms at 6-month follow-up (Table I). The frequency of CD in this JHS/EDS-HT population was compared by the standard Pearson chi-squared test with that in the Italian general population, using previously published data [Dubé et al., 2005]. Assuming a maximum CD prevalence of 1% in Italy [Menardo et al., 2006], the differential rate was statistically significant with a $P = 0.002$.

These findings indicate that, in Italy, CD is 10–20 times more common in JHS/EDS-HT compared to the general population. The reason as to why an autoimmune disorder like CD is more common in patients affected by a genetic condition apparently etiologically unlinked to the immune system remains unknown. The relatively small sample size could have influenced the exact estimation of this augmented prevalence, but the *P*-value strongly suggests that the association is not causal. Other genetic conditions, such as Turner, Down, Williams and velocardiofacial syndromes, show a paradoxical increased rate of CD and also in these cases the underlying mechanism remains elusive [Bonamico et al., 1998; Pueschel et al., 1999; Giannotti et al., 2001; Digilio et al., 2003]. JHS/EDS-HT is thought to be caused by mutations in gene(s) coding for components of the connective tissue. Recently, increased Ab titers against collagens I, III, V, and VI was demonstrated in CD [Dieterich et al., 2006]. This evidence prompted the authors to speculate for an increased risk for autoimmune connective tissue disorders among patients previously diagnosed with CD. In fact, the cross-linking

TABLE I. Clinical Features of the Patients' Sample and the Six JHS Cases With CD

Feature	Total	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6
Sex	25 F/6 M	F	F	F	F	M	M
Age at diagnosis (years)	10–54[a]	26	40	38	37	10	13
Congenital joint hypermobility	22/31	−	+	+	+	+	+
Clumsiness in infancy	15/31	−	−	−	−	+	+
Beighton score at evaluation	0–9[a]	6	2	7	4	8	7
Soft/velvety skin	25/31	−	−	−	+	+	+
Hyperextensible skin	8/31	−	−	−	+	−	+
Easy bruising	24/31	−	+	+	+	+	+
Chronic/recurrent arthralgias	31/31	+	+	+	+	+	+
Back pain	26/31	+	+	+	+	−	−
Chronic/recurrent myalgias	26/31	+	+	+	+	+	+
Recurrent sprains/strains	21/31	+	+	+	−	+	−
Recurrent dislocations	23/31	+	+	+	+	+	+
Chronic fatigue	28/31	−	+	+	+	+	+
Paresthesias	23/31	+	−	+	+	−	+
Recurrent tachycardias	22/31	−	+	+	+	−	+
Gastro-esophageal reflux	23/31	+	+	+	+	+	+
Chronic gastritis	13/31	+	+	+	+	−	−
Recurrent abdominal pain	19/31	+	+	+	+	−	+
Chronic diarrhea/constipation	23/31	+	+	+	+	+	+
Abdominal hernias	5/31	−	+	−	−	−	−
Positive AGA (IgA) screening	4/31	+	−	+	+	+	−
Positive AGA (IgG) screening	2/31	−	−	−	+	−	+
Positive EMA (IgA) screening	3/31	−	+	+	+	−	−
Positive EMA (IgG) screening	4/31	−	+	+	+	−	+
Positive anti-tTG (IgA) screening	4/31	+	+	+	+	−	−
Positive anti-tTG (IgG) screening	3/31	+	−	−	+	+	−
Jejunal villous atrophy	5/31	Ref.	+	+	+	+	+
Positive response to gluten-free diet	6/31	+	+	+	+	+	+

F, female; M, male; Pt, patient; Ref., refused.

[a]Reported values represent a range.

between gliadin peptides and interstitial collagen(s) may facilitate anti-collagen Ab formation and consequent chronic inflammation of the connective tissue. On the contrary, a constitutionally abnormal collagen (as expected in JHS/EDS-HT) might uncover an autoimmune reaction mediated by anti-collagen Ab, which, by virtue of the gliadin–collagen cross-linking, could facilitate the onset of CD in genetically predisposed subjects.

In conclusion, this preliminary study indicates an increased rate of CD in JHS/EDS-HT. In the absence of internationally approved guidelines for the management of JHS/EDS-HT and given the significant number of shared symptoms between JHS/EDS-HT and CD, AGA, EMA, and anti-tTG testing may be useful at first evaluation and in any further follow-up in presence of unexpected features compatible with CD. Jejunal biopsy should follow in case of positive Ab analysis. This relative high rate of CD in JHS/EDS-HT might contribute in explaining and, possibly, treating some disabling features, such as chronic constipation, chronic fatigue (including the chronic fatigue syndrome), and osteopenia/porosis, which are frequently encountered in JHS/EDS-HT. Further studies in larger samples with different geographic origins are expected in order to substantiate this evidence and translate it into the clinical practice.

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