RESEARCH LETTER

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Ehlers–Danlos Syndrome Hypermobility Type and the Excess of Affected Females: Possible Mechanisms and Perspectives

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TO THE EDITOR:

Joint hypermobility (JH) is a relative common finding in clinical practice, especially in rheumatology [Al-Rawi et al., 1985; Birrell et al., 1994]. A trained clinician may easily recognize JH by using specific sets of diagnostic criteria, the Beighton score being the most common [Beighton et al., 1973]. JH is often a benign trait and may regress with age [Grahame, 1999]. On the other hand, the term "joint hypermobility syndrome," which is now considered one and the same with the Ehlers–Danlos syndrome hypermobility type (EDS-HT) [Tinkle et al., 2009], refers to the concurrence of JH with additional musculoskeletal complaints without features of other well-defined connective tissue disorders [Hakim and Grahame, 2003]. While JH is deemed a multifactorial attribute, EDS-HT generally is an autosomal dominant or, more rarely, recessive trait [Wood, 1971; Grahame, 1999; Levy, 2010]. The molecular bases of JH and EDS-HT are still largely obscure, although approximately 5% of EDS-HT patients harbor homozygous or heterozygous mutations in the *TNXB* gene [Schalkwijk et al., 2001; Zweers et al., 2003].

Thus, in EDS-HT one should expect an equal number of affected males and females. Nevertheless, female patients are indisputably more common, especially among young adults and adults [Remvig et al., 2007; Castori et al., 2010]. Accordingly, in our cohort of 38 well-characterized EDS-HT index cases, 34 (89%) are females and 4 (11%) men. For nine of them, we demonstrated a positive family history by physical examination of available relatives. Among the 13 additional affected family members, 9 are females (69%) and 4 are males (31%). Therefore, although physical examination and interview of apparently unaffected relatives is capable of identifying a higher rate of affected males the skewed sex ratio remains undoubted [43 (84%) females vs. 8 (16%) males].

While female preponderance in EDS-HT is well known in clinical practice, the mechanisms underlying this female preponderance have not been well studied. Some authors postulate that a partial explanation could be the greater inclination of women to join to patients' support groups [Berglund et al., 2003]. However, this phenomenon is not valid in other countries, such as Italy, where most patients are still referred to dedicated services by general practitioners and other specialists without the mediatorship/intervention of patient associations. A further social factor may be the tendency of women to enter upon specific sport careers (such as gymnastics and ballet) which are facilitated by an increased joint motion and, in turn, worsen JH [McCormack et al., 2004]. This explanation does not fit well either with the great number of patients without similar sporting habits and/or suffering from very early disease manifestations.

Taken together, these data strongly suggest that the skewed sex ratio in EDS-HT is based on biological grounds. Alternative explanations can be put forward when considering the reasons as to why EDS-HT patients come to the clinician's attention. As JH per se is rarely considered a real problem by lay people, patients usually request evaluation when they manifest additional complaints, mainly including chronic pain and articular complications, such

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as recurrent dislocations, recurring inflammations of the peripheral ligamentous and muscular attachments, and precocious osteoarthritis. Consequently, it may be speculated that the excess of females is the result of an ascertainment bias related to sex-influenced processes of pain perception and/or joint stabilization.

Pain perception is a complex, still partly unknown process with a long evolutionary history. It is influenced by many factors. Among them, the role of gender in modulation of pain represents a growing field of interest for neurosciences with hundreds of articles published to date [Fillingim et al., 2009]. Different types of pain exist and, probably, EDS-HT patients complain of more than one form of pain [Castori et al., unpublished data]. However, muscle/deep pain reflects direct perturbation of the musculoskeletal system and, therefore, it is likely to be a common feature in EDS-HT. It is well known that, in the general population, women have greater frequency of musculoskeletal pain than men [Rollman and Lautenbacher, 2001]. This is confirmed by numerous experimental studies of muscle pain by using intramuscular injection of hypertonic saline and glutamate solutions [reviewed by Fillingim et al., 2009]. The demonstrated gender differences in brain activity evoked by deep/muscle pain may reflect divergences in emotional processing of noxious information in men and women, and, thus, suggests a major role for social conditioning and psychosocial factors in pain perception [Henderson et al., 2008]. However, other subcortical mechanisms involved in pain perception are influenced by sex. In fact, experimental muscle pain by hypertonic saline solution injection generates more efficient pain modulation, through a more intense activation of the diffuse noxious inhibitory control, in men than women [Ge et al., 2004]. Altogether, these differences in muscle pain perception may underlie the sex bias that is observed in many forms of chronic pain and rheumatologic conditions, such as EDS-HT.

Joint stability is determined by the efficiency and integrity of the musculoskeletal system and its neural regulation. It is well known that men tend to have larger muscles and greater absolute strength than women [Maughan et al., 1983; Kanehisa et al., 1994; Danneskiold-Samsøe et al., 2009]. This is partly mirrored by the morphologic evidence of larger striated muscle fibers in men [Toft et al., 2003]. However, sex-determined variations of the musculoskeletal system are most probably widespread. In fact, a wide range of studies showed significant gender differences in kinematics and biomechanics. In particular, a marked divergence has been demonstrated in the viscoelastic properties of tendon structures between men and women in various joints of the lower limbs [Kubo et al., 2003; Blackburn et al., 2009]. Thus, both muscle tone, and tendon and ligament stiffness are significantly influenced by sex. These factors cooperate to contribute to greater joint stability in men. Accordingly, this may explain the reduced rate of articular complications in men with EDS-HT.

Finally, accumulated data demonstrate that gender differences in pain perception and musculoskeletal system are considerably influenced by sex hormones [Bhasin and Storer, 2009; Fillingim et al., 2009]. At puberty, hormonal changes determine increased pain sensitivity in females and greater muscle strength in males [Trudeau et al., 2003] and this can also explain the higher gender bias in young adult and adult patients with EDS-HT.

These data suggest that EDS-HT is an autosomal dominant trait influenced by sex and that this gender bias cannot be simply explained by social or genetic (allelic) factors. This hypothesis is borne out in clinical practice. In fact, after the identification of a (female) patient with EDS-HT, examination and interview of parents, sibs and other close relatives often allows the detection of additional undiagnosed mutation carriers. EDS-HT may be suspected in male relatives who have never been considered affected simply because they do not manifest overt debilitating manifestations. Therefore, identifying the ''protective'' factors underlying the apparently reduced penetrance and milder clinical expression in males with EDS-HT may help in developing more appropriate approaches to treat symptomatic patients and, hopefully, to prevent complications in the asymptomatic ones. In addition, unravelling these mechanisms could significantly contribute to the understanding of the still-enigmatic knowledge gap between ''benign'' JH and EDS-HT. In keeping with this, it appears clear that the rehabilitation program for EDS-HT patients must be multidimensional. In the future, standard physical and pharmacological therapies should be intermingled with tailored programs, based on an in-depth knowledge of the physiological and psychological processes leading to symptom development in the ''hypermobile'' patient.

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