Ehlers–Danlos syndrome hypermobility type: a possible unifying concept for various functional somatic syndromes

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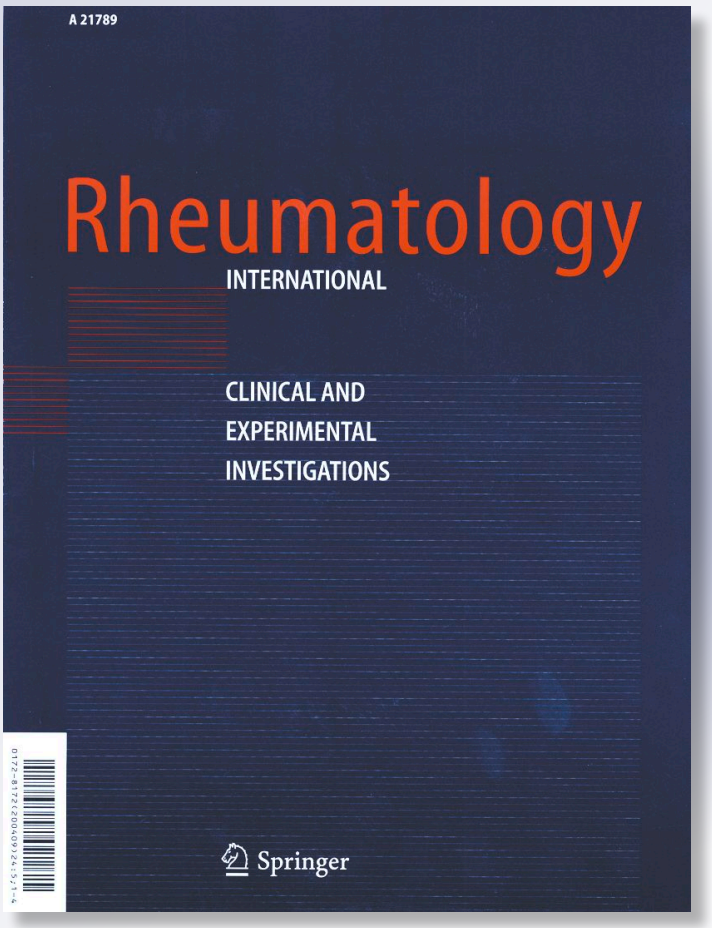

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LETTER TO THE EDITORS

Ehlers–Danlos syndrome hypermobility type: a possible unifying concept for various functional somatic syndromes

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To the Editor

We read with interest the paper by Carlesimo et al. [1] recently published in *Rheumatology International*. The authors highlighted the utility of ultrastructural study of the dermis in assessing Ehlers–Danlos syndrome hypermobility type (EDS-HT), formerly type III, and offered a rapid overview on what is the general thinking about this condition. EDS-HT, actually considered one and the same with the joint hypermobility syndrome (JHS), is a relatively common, frequently underdiagnosed heritable condition predisposing to chronic widespread musculoskeletal pain and a wide variety of articular and extra-articular features purportedly linked to constitutionally abnormal collagen. Actually, the diagnosis is clinical in essence and based on published diagnostic criteria [2, 3]. In line with the consolidated concept that the molecular basis of EDS-HT/JHS is still largely unknown except for a minority of patients mutated in *TNXB* and *COL3A1*, the authors stated that molecular screening for other variants of Ehlers–Danlos syndrome hypermobility type resulted negative. This is apparently in contrast with the notion that irregularities of collagen fibers of the type reported in this patient are more typical of the classic variant, which, in turn, is usually linked to mutations in *COL5A1* and *COL5A2*.

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The clinical overlap between EDS-HT/JHS and the classic type may be noteworthy in patients with minimal skin involvement, and on a practical perspective, the differential diagnosis may be performed only by direct evaluation of possibly affected relatives in order to detect typical cutaneous features, including papyraceous and/or hemosiderotic scars, molluscoid pseudotumors, and subcutaneous spheroids. This distinction is not simplistic, but probably reflects distinct etiopathological mechanisms leading to partially divergent disease evolution and course. In fact, as recently depicted, the natural history of EDS-HT/JHS is protean and may show at least three discrete phases resulting from the discordant progression of joint mobility, articular complications and extra-articular involvement [4, 5]. This probably mirrors complex interactions of a highly penetrant dominant gene with other constitutional and environmental factors, such as sex, ethnicity, sport activities, dietary habits, surgery and traumas, which may be determinant for the onset and worsening of specific complaints.

For a long time, EDS-HT/JHS has been considered a relatively benign condition with acute and/or chronic joint instability as its unique clinical consequence. Recently, more attention has been posed on the quality of life of these patients [6, 7], as well as on chronic pain and fatigue as the major determinants of such a deterioration of autonomy [8, 9]. However, accumulated experience on the management of EDS-HT/JHS patients illustrates a much more complex clinical picture. In particular, subjects with present or historical joint hypermobility appear more prone to develop a range of functional somatic syndromes, including fibromyalgia [10], chronic fatigue syndrome [11], complex regional pain syndrome [12], gastrointestinal functional disorder [13], pelvic organ prolapse [14] and orthostatic intolerance [15]. Possible additional relevant phenotypic components of EDS-HT/JHS are bladder pain syndrome (i.e., interstitial

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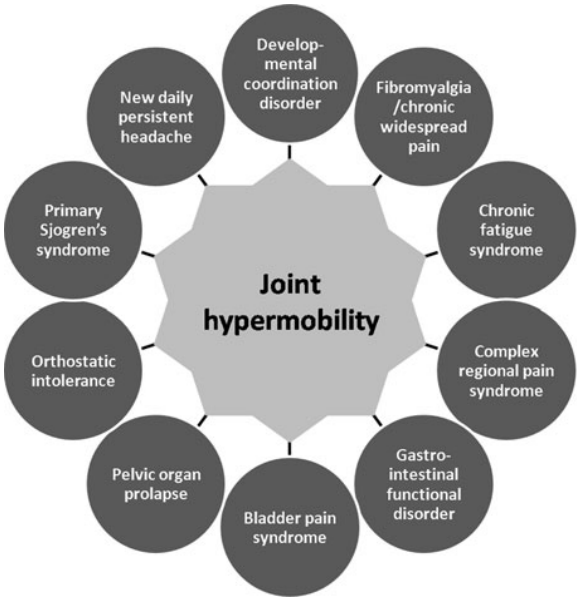

Fig. 1 Major clinical presentations of Ehlers–Danlos syndrome hypermobility type. Generalized joint hypermobility may represent the common milieau for various functional somatic syndromes with ubiquitous manifestations. This results from various studies suggesting or proving an increased frequency of these phenotypes in patients with generalized joint hypermobility. Conversely, joint hypermobility should be investigated in all patients showing mixed combinations of these functional disorders

Fig. 2 Patients with Ehlers–Danlos syndrome hypermobility type show abnormalities in practically all major systems, including gastrointestinal, cardiovascular, genitourinary and central/peripheral nervous systems. Most features may be explained by an underlying dysautonomic process. The pathogenic relationship between dysautonomia and congenital laxity of the connective tissue is still unknown. Future studies should be aimed at investigating the impact of impaired muscular and visceral proprioception as the missing link

cystitis), new daily persistent headache and primary Sjogren's syndrome (Castori, personal observation; Fig. 1), most of them representing direct or indirect manifestations of the underlying dysautonomia (Fig. 2) [16]. Notably, many of these presentations are the major reason of referral to the practitioner, who, in turn, is usually unprepared for considering joint hypermobility as a possible associated clinical sign linked to the underlying pathologic mechanism.

This result from compartmentalization of medicine which, on one hand, offers unexpected improvement for the understanding of organ/tissue-specific pathologic process and symptomatic treatments, but, on the other, limits the identification of connections between apparently unlinked dysfunctions in far away anatomic structures. This may be the case of a young congenitally hypermobile patient actually considered affected by developmental coordination disorder [17] and destined to ameliorate his/her clumsiness and motor performances with appropriate physical interventions, who, after perhaps a decade, could develop various extra-articular complications apparently unrelated to the past medical history. Thus, patients affected by EDS-HT/JHS urgently need more standardized management schedules and dedicated practitioners with a holistic approach and ready to rapidly intercepting subjects at risk and direct them in appropriate preventive programs.

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