INTRODUCTION

This issue of the American Journal of Medical Genetics Seminar Series Part C is dedicated to generalized joint hypermobility (gJHM), joint hypermobility syndrome (JHS), and Ehlers-Danlos syndrome, hypermobility type (EDS-HT). gJHM is the best known clinical manifestation of inherited defects of the connective tissue. On the other side, JHS and EDS-HT are actually considered one and the same from a clinical perspective by most practitioners and researchers (i.e., JHS/EDS-HT), and their molecular basis remains unknown. For decades, “non-syndromic” gJHM and JHS/EDS-HT have been thought to be simple clinical curiosities or an asset for the “affected” individual. In recent years, the attention on these partially overlapping phenotypes has increased, as they are now recognized risk factors for a series of non-communicable diseases and long-term disabilities. This series consists of 10 papers focused on three main topics, namely (i) assessment and differential diagnosis of children and adults with gJHM, (ii) systematic presentation of selected key non-articular manifestations of JHS/EDS-HT and actual perception of physiotherapy as the best therapeutic resource for this condition, and (iii) exploration of the available knowledge relating “congenital laxity of tissues” to various dysfunctions of the nervous system during development and adulthood. The contributors hope that this collection raises attention to this fascinating field of knowledge, which seems to have ramifications in virtually all medical disciplines.

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INTRODUCTION

This issue of the American Journal of Medical Genetics Seminar Series Part C is dedicated to generalized joint hypermobility (gJHM) and its most commonly associated syndromes, namely joint hypermobility syndrome (JHS) and Ehlers-Danlos syndrome (EDS), hypermobility type (EDS-HT). In the recent years, these conditions have attracted growing attention in various scientific fields which span from clinical research to molecular biology. In fact, while the explosion of molecular discoveries unraveled the molecular basis of an expanding number of rare connective tissue disorders featuring gJHM, the genetic cause(s) of its most commonly associated phenotypes remain(s) unknown. Hence, the attention of both clinicians and researchers is now moving to incorporate the obscure connections between gJHM and related extra-articular manifestations.

The series begins with papers dedicated to the differential diagnosis of gJHM in the pediatric age and adulthood. Dr. Colombi and collaborators focused on the wide range of hereditary connective tissue disorders presenting with prominent gJHM including almost all forms of EDS, osteogenesis imperfecta, Marfan syndrome,

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Loeys-Dietz syndromes, and arterial tortuosity syndrome which must be excluded before the attribution of a clinical diagnosis of JHS or EDS-HT. In the following paper, the international group composed of Drs. Donkervoort, Bonnemann, Loeys, Jungbluth, and Voermans present a guide for supporting the neurologist, as well as all other specialists encountering patients with gJHM in association with neuromuscular attributes, in the assessment and differential diagnosis of the double-jointed patient suspected of having an underlying muscular disorder. The number of hereditary neuromuscular disorders featuring gJHM is increasing and the boundaries with hereditary connective disorders is not always clear-cut. This happens because delayed attainment of motor milestones, muscle hypotonia and weakness are common ancillary findings in individuals with syndromic gJHM, also including JHS and EDS-HT. In addition, primary characteristics of hereditary neuromuscular and connective tissue disorders may coexist as pleiotropic manifestations of specific genes, such as COL6A1 and CHST14.

The series then moves on to three emerging issues concerning evaluation and management of patients with JHS and EDS-HT. The efforts of the Italian study group coalesced in a study on the mucocutaneous phenotype in 277 patients with JHS and EDS-HT. Although both the Villefranche and Brighton criteria for EDS-HT and JHS, respectively, identify specific diagnostic value for cutaneous involvement, its attribution remains based on vague definitions, such as “scarring” (Brighton) or “smooth, velvety skin” (Villefranche). In this work, the authors accurately scrutinized the extent and variability of cutaneous and mucosal involvement in JHS and EDS-HT with emphasis on their natural history. Subsequently, Dr. Castori and colleagues review the entire spectrum of gastrointestinal manifestations associated with gJHM, JHS, and EDS-HT. The results are critically analyzed in order to trace a reasonably comprehensive pathogenesis and to highlight hotspots to be applied in practice. A third paper is dedicated to the application of physical therapy in the management of JHS and EDS-HT. In this work, Dr. Rombaut and co-workers summarized the opinions of 325 Flemish physiotherapists on their knowledge and perception of EDS-HT. Gathered data are also used to define a shared therapeutic approach, which usually consists in a combination of education, reassurance, muscle strengthening and proprioceptive exercises, and core stability training.

The third cluster of papers explores the connections between gJHM and nervous system at different ages. Dr. Castori and co-authors present an exhaustive list of manifestations and possible mechanisms of cervical and head pain in EDS, with focus on JHS and EDS-HT. Particular attention is posed on the role of upper cervical spine instability to head and cervical pain, as well as to other more distant manifestations, which may relate to an underlying subclinical/intermittent compressive mielopathy. Dr. Sinibaldi and collaborators extensively reviewed data on psychopathological features associated with gJHM, JHS, and EDS-HT. They confirm a close relationship between gJHM and anxiety disorders and depression, but also highlight possible positive associations with attention deficit/hyperactivity disorder, obsessive-compulsive personality disorder, and autistic spectrum disorders. Psychopathology is discussed considering the role of the extracellular matrix in many nervous system and cognitive functions, as well as the use of an endophenotype-based approach in future research. Drs. Ghibellini, Brancati, and Castori scrutinized the literature searching for data exploring connections between gJHM and neurodevelopmental attributes. With the support of an exemplificative case, the authors summarized what is actually known concerning the effects of gJHM on coordination with in-depth speculations on possible pathogenesis and management. Dr. Celletti and co-workers emphasized the findings of previous works by presenting a cross-sectional study on 41 children with developmental coordination disorder. In this sample, the authors found a non-causal association between gJHM and a constellation of non-motor attributes, including attention deficit/hyperactivity disorder, atypical swallowing, and narrative difficulties. The series ends with an example of narrative medicine by Isobel Knight. With her three-faced nature of medical writer, Bowen therapist and woman affected by JHS and EDS-HT, she tells us her experience with the disease and practitioners, along a journey which testifies for the huge limits that the human mind experiences when faces with something unfamiliar.

gJHM

gJHM is actually taken in serious account and routinely investigated by practitioners involved in the evaluation and treatment of patients with hereditary connective tissue disorders. gJHM can be equally encountered in many skeletal dysplasias, which are indeed constitutional disorders affecting a specialized connective tissue (i.e., bone). As emphasized by Dr. Donkervoort and co-authors in the second paper of this series, the attention on gJHM is also growing among neurologists involved in neuromuscular disorders because an increasing number of hereditary myopathies and muscular dystrophies feature gJHM. Anyway, gJHM is still neglected, considered a harmless trait, or, perhaps, an asset for the patient by most professionals. The high rate of localized and widespread gJHM in the general population suggests, indeed, that the chance of developing some detrimental effect related to gJHM is relatively low in the single individual. However, when this happens the patient could be really affected by a multisystem disorder and, hence, exposed to additional risks and potential target of more tailored management schedules. In many cases, JHS and EDS-HT are the “default” diagnoses for patients with gJHM and additional features. This explains as to why much more emphasis is posed on the understanding of the pathophysiological basis of these, so apparently “benign” disorders.

JHS/EDS-HT

As recently accepted by many clinicians and researchers, and partly supported by
family studies, JHS and EDS-HT are not yet distinguishable on clinical grounds. This implies that JHS and EDS-HT should be prudently considered one and the same phenotype (i.e., JHS/EDS-HT), until molecular studies will solve the dilemma. However, at this time we cannot distinguish whether JHS and EDS-HT are two distinct disorders with a clearly different underlying molecular defect, or JHS and EDS-HT are relatively overlapping disorders which partially share their molecular basis (also within a non-Mendelian inheritance pattern), or rather they are two fully overlapping conditions with the same genetic underpinning (Fig. 1). Understanding this point could offer us the possibility not only to clarify the nosology and support with evidence our thinking of these disorders, but also to stratify patients for severity, prognosis and, hence, management protocols.

At the moment, we consider JHS/EDS-HT an autosomal dominant trait with nearly complete, age-dependent penetrance and variable expressivity. However, such an assumption, which is based on relatively weak observational data, is strongly influenced by the ascertainment procedure. In fact, literature is not clear and the various research groups that studied and contributed to define this entity in the last decades used a variable mixture, sometimes with ad hoc minor modifications of the Beighton score, Brighton criteria and Villefranche criteria. The direct consequence of such a heterogeneity is the low reproducibility of available information, as we cannot be sure that published clinical data belong to a really homogeneous condition. Anyway, after a few years spent in the evaluation and management of patients with JHS/EDS-HT, any practitioner recognizes the phenotypic continuum among this condition as a whole and the wide range of partially overlapping hereditary connective tissue disorders, such as various EDS subtypes, Marfan syndrome, Loeys–Dietz syndromes, and osteogenesis imperfecta. The molecular mechanisms underpinning such a phenotypic continuity remain obscure. We have not any strong proof for distinguishing between JHS/EDS-HT as a “simple” bridging phenotype of the other partially overlapping conditions without any separate molecular basis, and JHS/EDS-HT as a really distinct disorder caused by mutations in still unknown genes (Fig. 2). The coexistence of both hypotheses could still hold true considering an extremely variable genetic background ranging from Mendelian mutations in known genes associated with rarer hereditary connective tissue disorders, to the involvement of entirely novel genes. Difficulties are added by the protean natural history of JHS/EDS-HT, which presents with different symptoms and objective data at the various ages with strong variability in terms of range of joint mobility, rate of pain and other functional symptoms, degree and type of cutaneous involvement, and presence/absence of neurodevelopmental attributes (Fig. 3). Deciphering this “two-dimensional” heterogeneity (i.e., locus heterogeneity and age-dependent phenotypic variability—i.e., metatropism) is a hard task which needs an evolution of the classic approach to syndrome

Figure 1. Hypotheses on the relationships between joint hypermobility syndrome (JHS) and Ehlers–Danlos syndrome, hypermobility type (EDS-HT) within the broader group of generalized joint hypermobility (gJHM). Further comments are reported in the text.

Figure 2. Hypotheses on the relationship between the joint hypermobility syndrome/Ehlers–Danlos syndrome, hypermobility type (JHS/EDS-HT) and the partially overlapping conditions, including other Ehlers–Danlos syndromes (EDSs), myopathies with generalized joint hypermobility (gJHM), (some) skeletal dysplasias with gJHM, Marfan syndrome, Loeys–Dietz syndromes (LDSs), and osteogenesis imperfecta (OI). The concepts of JHS/EDS-HT as a bridging phenotype due to mutations in a mixture of known genes associated to partially overlapping disorders is compared to JHS/EDS-HT as a genetically distinct disorder. The coexistence of both hypotheses is still possible.
delineation and its molecular resolution. A new alliance between the growing resource of next-generation sequencing and a more in-depth understanding of the pathogenic contributors to clinical and subclinical variability in JHS/EDS-HT (and cognate disorders) should be encouraged.

Literature is full of case-control studies testing the possible association between gJHM and a wide range of musculoskeletal and non-musculoskeletal features. The emerging picture is confused, but some of these associations are reasonable and appear consistent on both statistical and pathophysiologic perspectives (Fig. 4). The mechanisms underlying these associations often remain speculative. Also in this field we cannot distinguish between different hypotheses, including pleiotropy (and, hence, some genotype-phenotype correlations), and pathogenic link. However, the existence of an unspecific pathophysiologic connection relating laxity of the connective tissue to the increased risk of developing related symptoms and dysfunctions seems a more likely explanation. Accordingly, we actually can register the non-casual association between gJHM and selected features among patients with non-syndromic gJHM, as well as with JHS/EDS-HT and rarer hereditary connective tissue disorders. The heterogeneity of the phenotypic subclasses presenting the same pattern of associated features stands for a convergent pathophysiologic pathway which may lay on the evolutionary origins of the connective tissue.

These considerations offer us the opportunity to delineate a somewhat hierarchical stratification of our population of interest as depicted in Fig. 5. As previously stated, a significant fraction of the general population presents gJHM or have presented gJHM in the past. Many of these subjects will remain asymptomatic for their entire life, while the remaining will develop some associated symptoms/disabilities. Among those who present symptomatic gJHM, an undefined fraction will respect criteria for being considered affected by a hereditary connective tissue disorder. This phenotypic subgroup is actually composed of most patients labeled with the attribution of JHS/EDS-HT, while the few remaining are indeed affected by rare hereditary connective tissue disorders, such as other EDS variants and Marfan syndrome. Every transition from each of these categories to the overhanging one represents a great clinical problem which needs much more energies for being understood. All these passages are complex in nature and are hardly resolved by the efforts of a single discipline. We discussed the

![Figure 3](image)

**Figure 3.** A diagram summarizing the protean natural history of the joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type. During the lifespan of every affected individual there is a high chance for a changing pattern in most features including range of joint mobility (i.e., Beighton score value) and neurodevelopmental difficulties which reduce, and rate of pain/functional symptoms and severity/rate of cutaneous involvement which, in turn, increase.

![Figure 4](image)

**Figure 4.** Spectrum of noncommunicable diseases associated with (generalized) joint hypermobility in humans. The ideogram includes only disorders with a relatively robust association with joint hypermobility (POTS—postural tachycardia syndrome).
expected improvements offered by the introduction of the new technologies together with a deeper understanding of the mechanisms underlying the sectional manifestations of laxity of tissues. This will surely help us in the classification and long-term management of the relatively few patients with a true syndromic diagnosis. The present collection contributes to tracing the actual state of the art of our knowledge concerning the clinical consequences of constitutionally impaired connective tissue in order to raise the attention on this field of knowledge, which could have ramifications in virtually all medical disciplines.

Figure 5. Ideogram showing the hypothetical stratification of different subpopulations in relation to presence/absence of generalized joint hypermobility (gJHM) and criteria for more defined hereditary connective tissue disorders (HCTDs), including joint hypermobility syndrome/Ehlers–Danlos syndrome, hypermobility type (JHS/EDS-HT), and rarer variants.