INVITED COMMENT

AMERICAN JOURNAL OF medical genetics PART A

The Lack of Clinical Distinction Between the Hypermobility Type of Ehlers–Danlos Syndrome and the Joint Hypermobility Syndrome (a.k.a. Hypermobility Syndrome)

Brad T. Tinkle,[1]* Howard A. Bird,[2] Rodney Grahame,[3] Mark Lavallee,[4] Howard P. Levy,[5] and David Sillence[6]

[1]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

[2]University of Leeds, West Yorkshire, United Kingdom

[3]University College Hospital, London, United Kingdom

[4]Memorial Sports Medicine Institute, South Bend, Indiana

[5]Johns Hopkins University, Baltimore, Maryland

[6]Connective Tissue Dysplasia Management Service, The Children's Hospital at Westmead, Westmead, New South Wales, Australia

Received 8 July 2009; Accepted 27 July 2009

Generalized joint hypermobility, defined using the Beighton criteria (≥5/9), can be seen in up to 40% of school-age children depending on race, ethnicity, gender, and prior physical training [Forleo et al., 1993; Larsson et al., 1993; Decoster et al., 1997; Rikken -Bultman et al., 1997; Remvig et al., 2007a]. However, generalized joint hypermobility may also be seen in many heritable connective tissue disorders (HCTDs), including but not limited to Ehlers–Danlos syndrome (EDS), osteogenesis imperfecta, and Marfan syndrome. In individuals presenting with generalized joint hypermobility, it is often desirable to determine whether this trait is a benign physiological variant or a manifestation of one of the HCTDs [Engelbert et al., 2003]. Clinical diagnostic criteria and molecular diagnostic testing help define many of the HCTDs. The most commonly used diagnostic criteria and nosology for the heterogeneous Ehlers–Danlos syndromes were defined by Beighton et al. in 1997 [Beighton et al., 1998]. Notably, however, there are no molecular diagnostic tests to rule in or out the hypermobility type of EDS, which is arguably the most common type.

Often, the most perplexing situation is when the vast majority of HCTDs can be ruled out using established criteria, leaving an individual with undiagnosed generalized joint hypermobility. Is this a familial trait and, if so, does it represent the higher end of the spectrum of normal joint mobility with little clinical consequence? Is it the so-called benign joint hypermobility syndrome (BJHS) that many would argue is not so benign [Adib et al., 2005]? Or does this represent the hypermobility type of EDS? Currently, the clinical criteria established to diagnose and distinguish BJHS or EDS hypermobility type are non-specific and not mutually exclusive [Remvig et al., 2007b].

The Brighton criteria (Table I) define an individual with BJHS as currently having, or having had a history of, generalized joint hypermobility [Grahame et al., 2000]. This takes into account the frequent observation that joint hypermobility decreases with age. Often, it is noted that an individual classified as having generalized joint hypermobility as a child or adolescent may not have a positive Beighton score as an adult. The Brighton criteria also use musculoskeletal pain as a major criterion for diagnosis of BJHS; thus, the more current terminology for this "not so benign" condition is the joint hypermobility syndrome (JHS). Minor criteria for diagnosis of the BJHS (also previously known as the hypermobility syndrome (HMS)) include joint instability or dislocations, a marfanoid body habitus, and soft subtly stretchy skin. Other HCTDs need to be excluded. However, there is no objective diagnostic testing of BJHS/

How to Cite this Article:
Tinkle BT, Bird HA, Grahame R, Lavallee M, Levy HP, Sillence D. 2009. The lack of clinical distinction between the hypermobility type of Ehlers–Danlos syndrome and the joint hypermobility syndrome (a.k.a. hypermobility syndrome).
Am J Med Genet Part A 149A:2368–2370.

*Correspondence to:
Brad T. Tinkle, M.D., Ph.D., Cincinnati Children's Hospital Medical Center, 3333 Burnet Ave, ML4006, Cincinnati, Ohio 45229.
E-mail: bradley.tinkle@cchmc.org

Published online 19 October 2009 in Wiley InterScience (www.interscience.wiley.com)
DOI 10.1002/ajmg.a.33070

TABLE I. The 1998 Brighton Criteria for a Diagnosis of Benign Joint Hypermobility Syndrome [Grahame et al., 2000]

Major criteria
- (1) Beighton score of ≥4/9
- (2) Arthralgia for >3 months in >4 joints

Minor criteria
- (1) Beighton score of 1–3
- (2) Arthralgia in 1–3 joints
- (3) History of joint dislocation
- (4) Soft tissue lesions >3
- (5) Marfan-like habitus
- (6) Skin striae, hyperextensibility, or scarring
- (7) Eye signs, lid laxity
- (8) History of varicose veins, hernia, visceral prolapse

For a diagnosis to be made either
- Both of the major criteria must be present
- OR one major and two minor
- OR four minor
- AND other disorders of connective tissue need be excluded

HMS and the diagnosis is based on clinical evaluation and history. The Beighton score is reliably reproducible but it is affected by race, ethnicity, gender, age, and prior physical training. Once again, for the adult, age and disuse may decrease one's joint mobility. The Brighton criteria attempt to take this into account by including a history of joint hypermobility as a major (or minor) criterion. Putting this into practice is subjective, as many patients will recall certain "acts" or "tricks" that they used to be able to perform but not necessarily the specific movements used in the Beighton criteria. However, by prior definition, BJHS/HMS is often more appropriate to use in the adult with chronic pain who may not have generalized hypermobility currently but only a history of it.

The hypermobility type of EDS is defined by generalized joint hypermobility (Beighton score ≥5/9) and soft, "velvety" skin that may or may not be appreciably hyperelastic (Table II). Of concern, assessment of soft or velvety skin is subjective and not scientifically reproducible [Remvig et al., 2009]. Often, EDS hypermobility type is the "default" diagnosis of children with generalized joint hypermobility and pain without signs or symptoms of another HCTD. Such children will frequently have a positive Beighton score and soft skin with no atrophic scarring. Whether or not this represents familial joint laxity without clinical consequences or the hypermobility type of EDS is often unclear. Indeed, the hypermobility type of EDS is not necessarily defined by the presence of clinical consequences such as joint dislocation, which is only a minor criterion.

TABLE II. Major and Minor Diagnostic Criteria for the Hypermobility Type of Ehlers–Danlos Syndrome [Beighton et al., 1998]

Major criteria
- (1) Beighton score of ≥5/9
- (2) Skin involvement (hyperextensibility and/or smooth, velvety skin)

Minor criteria
- (1) Recurring joint dislocations
- (2) Chronic joint/limb pain
- (3) Positive family history

It is the experience of many who see such patients that generalized joint hypermobility is found within families in a pattern consistent with autosomal dominant inheritance. However, younger children may be difficult to diagnose as it is often very difficult to distinguish familial joint laxity from the hypermobility type of EDS, and young children normally have relatively loose joints. It is also not uncommon to have one of the parents describing themselves as having had joint hypermobility when younger and currently complaining of chronic musculoskeletal pain and other symptoms which could be consistent with a diagnosis of either BJHS/HMS or hypermobility type EDS. Thus, multiple diagnoses may exist within the same family describing the same disorder of a heritable, autosomal dominant, generalized joint laxity essentially at different stages of their lives.

Could BJHS/HMS, familial joint laxity, and/or the hypermobility type of EDS exist within the same family? Certainly this is possible, but the frequency that this is observed would argue that familial joint laxity, EDS hypermobility type, and BJHS/HMS significantly overlap and are often clinically difficult to distinguish OR, in fact, represent a phenotypic continuum whose symptoms are more often related to activity and age rather than the underlying genetic defect. Indeed, Tofts et al. [2009] put forward the argument that clinically, we are interested in identifying those who have secondary consequences of their generalized joint hypermobility, such as pain or joint dislocations, for which they use the term "joint hypermobility syndrome" independent of the underlying diagnosis. Thus, the symptoms from generalized joint hypermobility (JHS) may occur in multiple HCTDs, including, but not limited to, EDS, BJHS/HMS, Marfan syndrome, and/or osteogenesis imperfecta.

We accept that this phenotypic spectrum likely represents multiple genetic etiologies and influences (genetic, hormonal, age, and environmental). Such patients warrant consideration of further diagnostic evaluation for one of the clearly defined HCTDs [Tofts et al., 2009]. When no other disorder can be elicited, such patients are often labeled as having BJHS/HMS or EDS hypermobility type as the "default diagnosis." While there is agreement that such patients often "fit" into a HCTD, without clearer delineations of terminology and diagnostic criteria, there can be honest disagreement on whether this should be described as BJHS/HMS or EDS hypermobility type.

Ultimately, a more appropriate "label" for this group is needed. As the genetic etiologies are discovered, we will likely find specific subgroups. In addition, by "lumping" all those with such strong phenotypic similarities, we may also be able to better define subtle differences in the phenotypic spectrum (such as those having a Marfan-like habitus) that may facilitate future differentiation based upon genotype.

It is our collective opinion that BJHS/HMS and EDS hypermobility type represent the same phenotypic group of patients that can be differentiated from other HCTDs but not distinguished from each other. Clinically, we serve this population better by uniting the two diagnostic labels. With this approach, we can strive to better define the phenotype and improve measurable outcomes of this

patient population. Furthermore, we recognize that it is important that, in those hypermobility patients who develop potentially debilitating symptoms of chronic fatigue or polyarthralgia, whatever the underlying cause, there should be prompt and appropriate intervention [Keer and Grahame, 2003].

REFERENCES

Adib N, Davies K, Grahame R, Woo P, Murray KJ. 2005. Joint hypermobility syndrome in childhood. A not so benign multisystem disorder? Rheumatology (Oxford) 44:744–750.

Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. 1998. Ehlers-Danlos syndromes: Revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). Am J Med Genet 77:31–37.

Decoster LC, Vailas JC, Lindsay RH, Williams GR. 1997. Prevalence and features of joint hypermobility among adolescent athletes. Arch Pediatr Adolesc Med 151:989–992.

Engelbert RH, Bank RA, Sakkers RJ, Helders PJ, Beemer FA, Uiterwaal CS. 2003. Pediatric generalized joint hypermobility with and without musculoskeletal complaints: A localized or systemic disorder? Pediatrics 111:e248–e254.

Forleo LH, Hilario MO, Peixoto AL, Naspitz C, Goldenberg J. 1993. Articular hypermobility in school children in Sao Paulo, Brazil. J Rheumatol 20:916–917.

Grahame R, Bird HA, Child A. 2000. The revised (Brighton) 1998 criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). J Rheumatol 27:1777–1779.

Keer R, Grahame R. 2003. Hypermobility syndrome, recognition and management for physiotherapists. Edinburgh: Butterworth Heinemann.

Larsson LG, Baum J, Mudholkar GS, Srivastava DK. 1993. Hypermobility: Prevalence and features in a Swedish population. Br J Rheumatol 32: 116–119.

Remvig L, Jensen DV, Ward RC. 2007a. Epidemiology of general joint hypermobility and basis for the proposed criteria for benign joint hypermobility syndrome: Review of the literature. J Rheumatol 34:804–809.

Remvig L, Jensen DV, Ward RC. 2007b. Are diagnostic criteria for general joint hypermobility and benign joint hypermobility syndrome based on reproducible and valid tests? A review of the literature. J Rheumatol 34:798–803.

Remvig L, Duhn PH, Ullman S, Kobayasi T, Hansen B, Juul-Kristensen B, Jurvelin JS, Arokoski J. 2009. Skin extensibility and consistency in patients with Ehlers-Danlos syndrome and benign joint hypermobility syndrome. Scand J Rheumatol 23:1–4.

Rikken-Bultman DG, Wellink L, van Dongen PW. 1997. Hypermobility in two Dutch school populations. Eur J Obstet Gynecol Reprod Biol 73: 189–192.

Tofts LJ, Elliot EJ, Munns C, Pacey V, Sillence DO. 2009. The differential diagnosis of children with joint hypermobility: A review of the literature. Pediatr Rheumatol 7:1.