RHEUMATOLOGY

Joint hypermobility and genetic collagen disorders: are they related?

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Joint hypermobility and genetic collagen disorders: are they related? If this same question had been posed a quarter of a century ago, the answer would have been very different from what is appropriate today. Conventional wisdom[1] has always favoured the view that "common" hypermobility merely represents the upper end of a Gaussian distribution of the "normal" joint range of movement. That view is now challenged by the notion that this variety of hypermobility, at least as far as it is seen from the clinic, may represent a departure from "normality". The inference is that it is a forme fruste of a genetic connective tissue disease (or heritable disorder of connective tissue (HDCT)). This does not, of course, exclude the possibility that "common" hypermobility, such as is seen in musicians and dancers, may be non-pathogenic polymorphisms, as a result of minor variations in extracellular matrix genes such as collagens, elastin, fibrillins, etc. Other variations might be in different, more interactive regions of the protein and are then pathological.

Joint hypermobility

A hypermobile joint is one whose range of movement exceeds the norm for that individual, taking into consideration age, sex, and ethnic background. The maximal range of movement that a joint is capable of is determined by the tightness or otherwise of the restraining ligaments. Thus, the primary cause of hypermobility is ligamentous laxity. This is inherent in a person's make up and is determined by their fibrous protein genes. Of particular importance in this respect are the genes that encode collagen, elastin, and fibrillin.

In general, joint laxity is maximal at birth, declining rapidly during childhood, less rapidly during the teens, and more slowly during adult life.[2] Women are generally more lax jointed than men at all ages and there is wide ethnic variation. Epidemiological studies have shown that hypermobility (depending on the criteria used) is seen in up to 10% of individuals in Western populations. In other populations it has been recorded to be as high as 25%.[3 4] Earlier studies looked at generalised hypermobility. We now know that pauci-articular (by definition, less than five joints involved) is even more highly prevalent than the polyarticular variety.[5]

Acquired hypermobility

Joint range can also be increased into the hypermobile range by the sheer hard work of training. Ballet dancers who are not inherently lax jointed need to acquire hypermobility in certain joints to perform their art. Once they have achieved this, their basically "normal" tissues protect them against injury (see below). Generalised joint laxity may follow in the wake of irreversible changes that occur in connective tissues in certain acquired diseases including acromegaly, hyperparathyroidism, chronic alcoholism, and rheumatic fever.[6]

Recognition of hypermobility

The most widely used method is to test whether the patient can perform a series of manoeuvres (Beighton score) (table 1).[7]

Unfortunately, many clinicians omit these tests from their examination, so that hypermobility is often overlooked and its importance passes undetected. The Beighton score is a useful starting point, but it has a number of shortcomings. For instance, it gives no indication of the severity of the hypermobility. It merely indicates how widely it is distributed throughout the body. There is also a risk that in pauci-articular involvement the hypermobility could pass unnoticed. Other areas worth looking at include the proximal and distal interphalangeal joints, shoulders, cervical spine, hips, patellae, ankles, hind and forefeet, and metacarpophalangeal joints.

"The benign joint hypermobility syndrome"

When hypermobility becomes symptomatic, the "hypermobility syndrome" is said to exist. Because of its favourable prognosis by comparison with other more serious HDCTs, the

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Table 1   *Nine point Beighton hypermobility score*

The ability to	Right	Left
1. Passively dorsiflex the fifth metacarpophalangeal joint to ⩾ 90°	1	1
2. Oppose the thumb to the volar aspect of the ipsilateral forearm	1	1
3. Hyperextend the elbow to ⩾ 10°	1	1
4. Hyperextend the knee to ⩾ 10°	1	1
5. Place hands flat on the floor without bending the knees	1	
Total possible score	9	

One point can be gained for each side for manoeuvres 1–4 so that the hypermobility score will have a maximum of 9 points if all are positive.

term benign joint hypermobility syndrome is also used. Lax joints are likely to be less stable, to sublux or dislocate, and are generally more susceptible to the effects of trauma. Soft tissues too are less resilient, so that ligament and muscle tears and tendon–osseous attachment lesions such as epicondylitis and plantar fasciitis may occur with increased frequency. The spine is particularly susceptible and lumbar disc prolapse, pars interarticularis defects, and even spondylolisthesis occur with increased frequency. Paediatricians will know that backache occurring in children or teenagers should always raise a suspicion of hypermobility.

On the other hand, many (perhaps most) hypermobile subjects have few or no problems and enjoy a symptom free life. Others seem to have problems at certain times of their life and not at others. It is not always possible to pinpoint the determining factors, although a change in lifestyle, particularly involving unaccustomed physical exercise, is the usual precipitating factor. There is increasing evidence that hypermobility is an important (yet largely unacknowledged) risk factor in the pathogenesis of osteoarthritis.[8][9] This relation could be a simple mechanical overuse phenomenon, but might also be caused by errors in genes such as collagens IX (COL 9A1, 9A2, and 9A3), XI (COL 11A1 and 11A2), and V (COL 5A1 and 5A2).

Positive benefits of hypermobility

There are undoubted benefits. The inherently greater agility enables the hypermobile subject to perform a number of physical activities with greater ease. These include ballet dancing,[10] gymnastics,[11] and acrobatics. Thus, hypermobility appears to act as a positive factor in selection into ballet school, at least as far as girls are concerned.[10] The predisposition to the effects of injury, however, means that for many budding ballerinas these early benefits are short lived.[12] Any child presenting with musculoskeletal symptoms (or even those without) who has a history of performing contortionist "party tricks" or of having been attracted into ballet, gymnastics, or acrobatics at an early age is likely to be hypermobile. Research has shown that violinists, flautists, and pianists (of all ages) with lax finger joints suffer less pain than their less flexible peers.[13]

The genetic collagen disorders

In the context of joint hypermobility, the HDCTs are usually taken to comprise Marfan syndrome, Ehlers-Danlos syndrome, and osteogenesis imperfecta. These are all very well known diseases with an established place in the medical literature since they were first described over a century ago. At first glance they are very different diseases, as their cardinal features would suggest, namely: marfanoid habitus, aortic aneurysm, and ectopia lentis in Marfan syndrome; skin hyperextensibility and joint laxity in Ehlers-Danlos syndrome; and brittle bones and blue sclerae in osteogenesis imperfecta. Closer examination of the clinical features reveals that there is considerable overlap between them, and the so called cardinal features are by no means uniquely linked to the disease with which they are most closely associated. Thus, stretchy skin also occurs in Marfan syndrome,[14] marfanoid habitus is also seen outside the Marfan syndrome,[15] and osteoporosis is also found in the Ehlers-Danlos syndrome.[16] Joint hypermobility is a feature common to all of them, although it can vary enormously in degree. The degree of clinical overlap as seen in the three major diseases is shown in tables 2–4. A valiant effort was made to develop an internationally agreed classification when "The Berlin nosology" was published in 1986.[17] According to this classification, familial articular hypermobility syndrome (by inference the benign joint hypermobility syndrome) is distinguished from Ehlers-Danlos syndrome type III by the normal skin in the former, compared with the extensible but not fragile skin found in Ehlers-Danlos syndrome type III. It is the author's contention that this distinction is no longer absolute, and a provisional set of diagnostic criteria for the benign joint hypermobility syndrome has been proposed[18] and validated.[19] The Berlin criteria for the diagnosis of Marfan syndrome have also been revised recently.[15]

Table 2   Clinical spectrum of Marfan's syndrome

Site	Cardinal features	Symptoms	Effects
Joints	Hypermobility	Arthralgia	Instability
		Dislocation	Soft tissue trauma
Skeleton	Marfanoid habitus	Slender extremities	Scoliosis
		Pectus deformities	Arachnodactily
Skin	Hyperextensibility	Thinning	Papyraceous scars
		Striae atrophicae	Easy bruising
Eyes	Ectopia lentis	Visual problems	
Vasculature	Aortic dilatation	Aneurysm	
	Mitral valve	Prolapse	SBE

SBE, subacute bacterial endocarditis.

Table 3   Clinical spectrum of Ehlers-Danlos syndrome

Site	Cardinal features	Symptoms	Effects
Joints	Hypermobility	Arthralgia	Instability
		Dislocation	Soft tissue trauma
Skeleton	Osteoporosis	Scoliosis	Deformity
		Fracture	
Skin	Hyperextensibility +	Thinning	Violaceous papyraceous scars
		Striae atrophicae	
		Molluscoid pseudotumours	Bruising and haematoma
			Subcutaneous spheroids
Vasculature	Mitral valve	Prolapse	SBE
	Intracranial (Ehlers-Danlos syndrome type IV)	Aneurysm	Subarachnoid haemorrhage
Muscles		Hernia	Rectal/uterine prolapse
		Intestinal/bladder diverticula	Neuromyopathy

SBE, subacute bacterial endocarditis.

Table 4   Clinical spectrum of osteogenesis imperfecta

Site	Cardinal features	Symptoms	Effects
Joints	Hypermobility	Arthralgia	Instability
		Dislocation	Soft tissue trauma
Skeleton	Osteoporosis++	Fracture	Deformity
Skin	Hyperextensibility	Thinning	Papyraceous scars
		Striae atrophicae	Easy bruising
Eyes	Blue sclera		
Vasculature	Mitral valve	Prolapse	SBE

SBE, subacute bacterial endocarditis.

Table 5 Benign joint hypermobility syndrome (Ehlers-Danlos syndrome type III)

Site	Cardinal features	Symptoms	Effects
Joints	Hypermobility	Arthralgia	Instability
		Dislocation	Soft tissue trauma
Skeleton	Marfanoid habitus	Slender extremities	Scoliosis
	Osteoporosis (low bone	Pectus deformities	Arachnodactily
	mineral density)	Fracture	Deformity
Skin	Hyperextensibility	Thinning	Papyraceous scars
		Striae atrophicae	Easy bruising
Eyes	Lid laxity		
	Blue sclera (occasionally)		
Vasculature	Varicose veins		
Muscles		Hernia	Rectal/uterine prolapse

The impact of molecular genetics on diagnosis

It is a reasonable expectation that laboratory diagnosis will soon be on hand to assist in diagnosis. Recent progress in this field has been impressive. Mutations in the fibrillin genes, FIB 1 and FIB 2, respectively, have been linked to Marfan syndrome and congenital contractural arachnodactily, a related disorder.[20] Similarly, over 200 separate mutations in genes encoding type 1 collagen, COL 1A1 and COL 1A2, are known in osteogenesis imperfecta.[21] About 80 mutations have been described in COL 3A1.[22] New associations are being described with increasing frequency. Nevertheless, it will be some time before the genetics laboratory will be able to make a meaningful contribution to diagnosis except in a few specific instances. Segregation analysis comparing the inheritance of collagen gene markers and benign joint hypermobility syndrome in two extended families excluded the genes encoding COL 3A1, COL 5A2, and COL 6A3, and found no suggestion of strong linkage with either COL 1A1 or COL 1A2.[23] Rather than being monogenic, benign joint hypermobility syndrome is more likely to have multiple causes involving many extracellular matrix components.

Does joint hypermobility exist in "normal" subjects who do not have a genetic connective tissue disease?

The three classic diseases under discussion—Marfan syndrome, Ehlers-Danlos syndrome, and osteogenesis imperfecta—are, by and large, rare diseases. In contrast, hypermobility (provided it is looked for) is seen commonly in clinical practice. It constitutes a large proportion of referrals to rheumatic clinics catering for both adults and children with musculoskeletal symptoms.[24 25] These symptoms are very similar to those seen in the aforementioned diseases, but they are often less severe, mirroring the degree of tissue laxity, which is less in "simple" hypermobility. Symptomatic hypermobile subjects are deemed to have the benign joint hypermobility syndrome.[26] As described originally, this was considered to be an affliction limited to the musculoskeletal system. Thirty years on the picture is looking different. Not only has the clinical syndrome been delineated more precisely, there is now a consensus that benign joint hypermobility syndrome is a multisystem disorder with features that overlap with Marfan syndrome, Ehlers-Danlos syndrome, and osteogenesis

imperfecta.[27] The diagnostic criteria for the benign joint hypermobility syndrome include such features as skin which is hyperextensible, shows striae, and heals poorly, leaving papyraceous scars.[18] Many authorities now accept that benign joint hypermobility syndrome is identical to Ehlers-Danlos syndrome type III. Table 5 shows the clinical spectrum.

Clinical overlap between the genetic collagen disorders and the hypermobility syndrome

Tables 2–5 show that clinical symptoms tend to overlap among this group of disorders. The fact that this tendency includes the benign joint hypermobility syndrome is strong presumptive evidence that this syndrome is, indeed, a member of the HDCT group of diseases. However, if this is so, it is a common and relatively benign one. On this basis, the "hypermobility" and the "genetic collagen disorders" of the title can be said to be related.

It should be emphasised, however, that data shown in table 5 are derived from the clinic and hence highly selected. The key question as to whether there are hypermobile subjects (symptomatic or otherwise) who do not show overlap features—that is, they have "normal" connective tissues—must await the results of the necessary epidemiological studies.

Evidence that joint hypermobility and genetic collagen disorders might be unrelated

In 1990 a rather surprising discovery was made in Denmark. In a controlled study involving skin analgesia, eight patients with Ehlers-Danlos syndrome type III were found to be resistant to lignocaine administered either by intradermal infiltration or topical cream.[28] The evaluation was performed by estimating sensory and pain thresholds to brief argon laser stimuli and the depth of controlled needle insertion. A second study from the same group published the following year using an identical method compared the effect in seven patients with Ehlers-Danlos syndrome type III with those in 10 patients with hypermobility and 15 controls. The thresholds were significantly lower in the patients with Ehlers-Danlos syndrome than in the other two groups.[29] The authors concluded that this is a useful method of distinguishing the two conditions from one another. This, of course, begs the question as to whether they are two distinct conditions. The authors assumed that they were. Unfortunately, the criteria for selection in the study were not documented clearly. In particular, it is not clear how the patients with Ehlers-Danlos syndrome type III were distinguished from the hypermobility patients. In the intervening seven years this work has neither been confirmed nor refuted. Were it to be repeated, this time with rigorous attention to clinical selection, it could, perhaps, carry the key to the solution of the Editor's conundrum posed in the title.

Summary

The HDCTs constitute a heterogeneous group of rare genetically determined diseases, the best known of which are Ehlers-Danlos and Marfan syndromes and osteogenesis imperfecta. Hypermobility is a feature common to them all, but it is also a feature that is highly prevalent in the population at large. Symptomatic hypermobile subjects (whose symptoms are attributable to their hypermobility) are said to be suffering from the benign joint hypermobility syndrome, which has many features that overlap with the HDCTs. It is not yet known whether there is a variety of hypermobility (symptomatic or otherwise) that is not part of a connective tissue disorder.

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