

Hypermobility syndromes from the clinician's perspective: an overview

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ABSTRACT

Symptomatic generalized hypermobility is a frequent occurring condition among patients referred to the rheumatologist or other medical specialist. In a subset of patients, a further classifying diagnosis of a specific syndrome can (and should) be made, based on pattern recognition and knowledge of the spectrum of hypermobility syndromes. Diagnostic clues are the patient's and family history and signs at physical examination, including skin abnormalities. It is especially important to recognize hypermobility syndromes with potentially life threatening complications.

Genetic testing is only available for some syndromes; is only indicated if there is a reasonable pretest probability regarding a specific syndrome, especially if this syndrome can have life-threatening complications.

The therapy is for the major part of syndromes only symptomatic; key features of management are education and physical exercises; joint surgery is to be avoided.

Keywords: Hypermobility; Ehlers-Danlos; Marfan; Loeys-Dietz; Deconditioning

INTRODUCTION

Hypermobility is defined as an increased range of movement in one or more joints. When many joints are hypermobile in an individual, we speak of **generalized hypermobility**, a relatively common condition. There are several classification criteria and scores sets for this condition - those of Beighton and Bulbena are presen-

ted in Table I^{1,2}.

Individuals with generalized hypermobility may be asymptomatic. Often, however, joint hypermobility is accompanied by musculoskeletal symptoms such as pain in joints, ligaments, entheses (attachment sites of tendons or ligaments to the bone) and muscles - this is usually referred to as **symptomatic hypermobility**. In addition, joint hypermobility can be associated with a wider spectrum of symptoms and signs reflecting involvement of other organs and organ systems, attributable to defective and lax connective tissues. In such cases the term "**hypermobility syndrome**" is appropriate.

Most individuals with generalized hypermobility do not stand out clinically and do not meet criteria of a specific syndrome. Others with generalized hypermobility may meet criteria of a specific defined syndrome, some of which may have life-threatening complications, making it important not to overlook these diagnoses.

The aim of this paper is to provide the rheumatologist and other medical specialists an overview of the broad spectrum of symptomatic hypermobility syndromes they may be confronted with, as a guidance in daily practice. Clinical aspects, with emphasis on musculoskeletal problems, are described and clues for diagnosis and management are provided.

EPIDEMIOLOGICAL ASPECTS

Generalized hypermobility may actually be a variant of normal mobility, along the upper tail of the Gaussian curve describing the range of motion of normal joints in the population, just as individuals can be (very) short or tall. In general, joint mobility and, thus, hypermobility, decreases with increasing age, is more common in females than males and occurs more often in some racial groups, such as Asian when compared to Caucasians³.

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TABLE I. BEIGHTON AND BULBENA CRITERIA AND SCORES TO ASSESS GENERALIZED HYPERMOBILITY

Criteria	Beighton score*	Bulbena score
<i>Upper extremities, passive movements</i>		
External rotation in the shoulder > 85°		1
Hyperextension of the elbow >10°	1	1
Apposition of thumb to flexor aspect of forearm	1, if touching	1 at distance < 21 mm
Dorsiflexion of fifth metacarpophalangeal joint > 90°	1	1
<i>Lower extremities, passive movements</i>		
Hip abduction > 85°		1
Knee flexion allows heel to contact buttock		1
Hyperextension of the knee > 10°	1	
Shift of patella to lateral side of tibia		1
Dorsiflexion of the ankle > 20°		1
Dorsiflexion of the first metatarsophalangeal joint > 90°		1
<i>Spine, active movement</i>		
Placing flat hands on the floor with straight legs	1	

Beighton score: range 0-9, *each criterion scores 1 point for each side of the body, if present, with exception of placing flat hands on the floor; generalized hypermobility if total score ≥ 5 .

Bulbena score: each criterion scores 1 point if bilaterally present; range 0-9; generalized hypermobility if total score ≥ 5 in males and ≥ 6 in females.

Many young individuals, especially among those performing ballet or gymnastics, would probably meet the criteria of generalized hypermobility if they were screened. In some sports, hypermobility may be an advantage, but it may also be a liability due to the increased risk of injuries^{4,5}. Reassuringly, a study in professional dancers concluded that joint hypermobility was not associated with a higher risk of injuries when assessed prospectively⁶. However, this observation does not rule out an increased risk of injury associated with hypermobility in the (less trained) general population. In fact, those more prone to injuries may have fallen short of a desired professional sports career.

People presenting for medical care with symptomatic hypermobility are most probably a subgroup of those with hypermobility in the population. Furthermore, not all cases of this subgroup will meet criteria for generalized hypermobility. An even smaller number will meet criteria for a specific hypermobility syndrome, such as benign joint hypermobility syndrome (BJHS; for criteria see Table II) or Ehlers Danlos syndrome (EDS), a group of hypermobility syndromes with as key features generalized hypermobility and lax skin (Table III). A description of all EDS-types is beyond the scope of this paper.

Exact prevalence estimates for EDS and BJHS are difficult to make for two main reasons. First, there is

the problem of recognition: not all individuals with generalized hypermobility have relevant symptoms and reach medical attention. If joint hypermobility and skin manifestations are mild, they might stay unrecognized. As a consequence, estimates on the prevalence of EDS types and BJHS depend on whether they are based on clinical reports of the syndromes, or on screening studies in populations. In the latter case, the prevalence estimates will be probably more accurate and higher. A study in a general dermatology population revealed that mild variants of EDS were present in 9% of this population⁷. Second, there is the problem of current classifications: an almost complete overlap exists between the signs, symptoms and classification criteria of EDS hypermobility type and those of the more frequently occurring BJHS (Table IV)⁸ and both show a similar familial hereditary pattern.

The prevalence of BJHS is estimated to range from 10–30% in adults, and from 10–15% in male youngsters between 11–17 years and up to 20–40% in girls of this age group⁹. The prevalence of EDS, of which the hypermobility type is the most frequent, is most probably higher than the current estimate of 1:5,000¹⁰. Marfan syndrome is an autosomal dominant hereditary connective tissue disorder with a prevalence of about 1:5000; 25% of the cases seems to be caused by a new mutation^{11,12}.

TABLE II. THE REVISED BRIGHTON 1998 CRITERIA FOR BENIGN JOINT HYPERMOBILITY SYNDROME (BJHS)¹**Major criteria**

1. A Beighton score $\geq 4/9$ (either currently or historically)
2. Arthralgia for >3 months in four or more joints

Minor criteria*

1. A Beighton score of 1–3/9 (0–3 if aged ≥ 50 year)
2. Arthralgia (≥ 3 month) in one to three joints, or back pain (≥ 3 month), or spondylosis, spondylolysis/spondylolisthesis
3. Dislocation/subluxation in more than one joint or in one joint on more than one occasion
4. Three or more soft tissue lesions (e.g. epicondylitis, tenosynovitis, bursitis)
5. Marfanoid habitus (tall, slim, arm span to total height ratio >1.03 ; upper segment to lower segment ratio <0.89 , arachnodactily (+Steinberg/wrist signs))
6. Abnormal skin: striae or hyperextensibility, thin cutis, or papyraceous scarring
7. Eye signs: drooping eyelids or myopia, or antimongoloid slant
8. Varicose veins or hernia or uterine/rectal prolapse

BJHS is diagnosed in the presence of either two major criteria, one major and two minor criteria, or four minor criteria. Two minor criteria will suffice where there is an unequivocally affected first-degree relative. BJHS is excluded by presence of Marfan syndrome or Ehlers–Danlos syndrome (other than the Ehlers–Danlos syndrome hypermobility type). Criteria major 1 and minor 1 are mutually exclusive, as are major 2 and minor 2.

*Other, neurophysiological signs include impairment of joint proprioception, lack of efficacy of local anesthetics, and autonomic dysfunction^{2,3}.

TABLE III. GHENT UPDATED CLASSIFICATION -ACCORDING TO GENETIC RESEARCH OF EHLERS–DANLOS SYNDROME (EDS)⁴

EDS type (old name)	Inheritance*	Protein	Gene	Distinguishing features ⁵ **
Classic (type I and II) #	AD	Procollagen type V	COL5A1/-A2	Wide, atrophic scars
		Procollagen type I	COL1A1	
Classic-like	AR	Tenascin-X	TNX-B	No atrophic scars
Hypermobility (type III) #	AD	?	?	None specific
		Tenascin X	TNX-B	
Vascular (type IV) #	AD	Procollagen type III	COL3A1	Arterial, intestinal & uterine rupture
Vascular-like	AD	Procollagen type I (R-to-C)	COL1A1	Arterial rupture
Cardiac-valvular	AR	2(I) collagen chain	COL1A2	Cardiac valve insufficiencies
Kyphoscoliotic (type IV) #	AR	Lysyl hydroxylase-1	PLOD1	Scoliosis at birth, progressive; microcornea
Musculocontractural	AR	Dermatan-4-sulfotransferase-1	CHST14	Muscular hypotonia, contractures
Spondylocheirodysplastic	AR	ZIP13	SLC39A13	Thin skin, skeletal dysplasia
Brittle cornea syndrome	AR	ZNF469	ZNF469	Eye abnormalities
		PRDM5	PRDM5	Eye abnormalities
Arthrochalasia (type VIIA & -B) #	AD		Procollagen type I ^{###}	COL1A1/-A2 Congenital hip dislocation
-EDS/OI ^{###} overlap	AD	Procollagen type I ^{####}	COL1A1/-A2	Bone fragility
Dermatosparaxis (type VIIC) #	AR	Procollagen-I-N-proteinase	ADAMTS2	Large inguinal & umbilical hernias

*AD, autosomal dominant; AR, autosomal recessive; ** all types characterized more or less by generalized hypermobility and lax skin; distinguishing features vary between patients;

#types of Villefranche classification (old term); other types: updated; ### OI: osteogenesis imperfecta; ### deletion of N-propeptide cleavage site;

delay in N-propeptide cleavage

TABLE IV. SIMILARITY OF VILLEFRANCHE CRITERIA FOR EDS HYPERMOBILITY TYPE AND BRIGHTON CRITERIA FOR BJHS*

	EDS hypermobility type 1997 Villefranche criteria ⁶	BJHS 1998 Brighton criteria ¹
Major criteria	Generalized joint hypermobility (score 5/9)	Generalized joint hypermobility: Beighton score of 4/9 or greater (either currently or historically)
	Skin involvement (hyperextensibility and/or smooth velvety skin)	Arthralgia for longer than 3 months in 4 or more joints
Minor criteria	Recurring joint dislocations	Dislocation/subluxation in > 1 joint, or in 1 joint > 1 time
	Chronic joint/limb pain	Abnormal skin: striae, hyperextensibility, or thin skin, or papyraceous scarring

* General joint hypermobility is a major criterion for both sets; (sub)luxations an identical minor criterion. The other signs and symptoms appear as major criteria in one set and as minor sign in the other

GENERAL SYMPTOMS, SIGNS AND COMPLICATIONS OF HYPERMOBILITY SYNDROMES

Patients with symptomatic hypermobility syndromes may share many clinical characteristics, typically including chronic musculoskeletal pain, fatigue, signs of autonomic dysfunction, and joint (sub)luxation. Pain and fatigue are the dominant symptoms. In the following section we discuss the most prevalent symptoms and signs the clinician is confronted with and their associations

PAIN

There is an increased prevalence of arthralgia (joint pain), chronic generalized myalgia and fibromyalgia (chronic generalized pain in muscles and joints) in hypermobile children and adults^{3,8,13-19}. In adults, hypermobility is also associated with back pain^{17,20}. Perhaps surprisingly, the basis of the association of hypermobility and pain is not established. The most consensual view is that pain is due to repetitive strain, sprain and microtraumata of muscles and ligaments by the abnormal range-of-motion permitted by hypermobile joints, aggravated by diminished joint proprioception, position sense²¹⁻²³, and decreased passive muscle tension²⁴. Pain is also related with anxiety and depression, both of which seem to be more prevalent in EDS as well as in BJHS²⁵⁻²⁷. It is commonly believed that chronic pain elicits depressive feelings and that depression has an amplifying effect on chronic pain and fatigue, leading to a vicious circle. These latter symptoms could lead to reduced physical activity and thus physical de-

conditioning (reduced physical condition), aggravating liability to injury, chronic pain and fatigue and initiating a downward negative spiral.

Furthermore, there seems to be a primary involvement of muscle in EDS hypermobility type: muscle weakness has been found in the absence of reduced muscles mass, which would have been present if muscle weakness was the results of reduced physical activity only²⁸. A hypothetical model on pain, including fatigue and physical deconditioning is depicted in Figure 1.

INSUFFICIENT EFFECT OF LOCAL ANALGESICS

An insufficient effect of local analgesics either by intradermal injection or as topical cream application has been reported in patients with EDS hypermobility type. This was thought to be due to the lax connective tissues in the skin allowing too much dispersal of the analgesic^{29,30}. However, the dispersal of a radioisotope labeled solution following deep dermal injection did not differ between EDS patients and healthy controls in a small study³¹. So, the reason for the insufficient effect of local analgesics is not yet known.

It was suggested that this phenomenon could be used as a diagnostic test to discriminate between EDS hypermobility type and BJHS³⁰, but further study is warranted.

FATIGUE

Hypermobility syndromes are associated with increased fatigue³²⁻³⁴. A hypothesis is that fatigue is a symptom of autonomic dysfunction or dysautonomia, described below^{33,34}. Others suggest that the hyperlaxity of joint ligaments demands increased vigilance, mus-

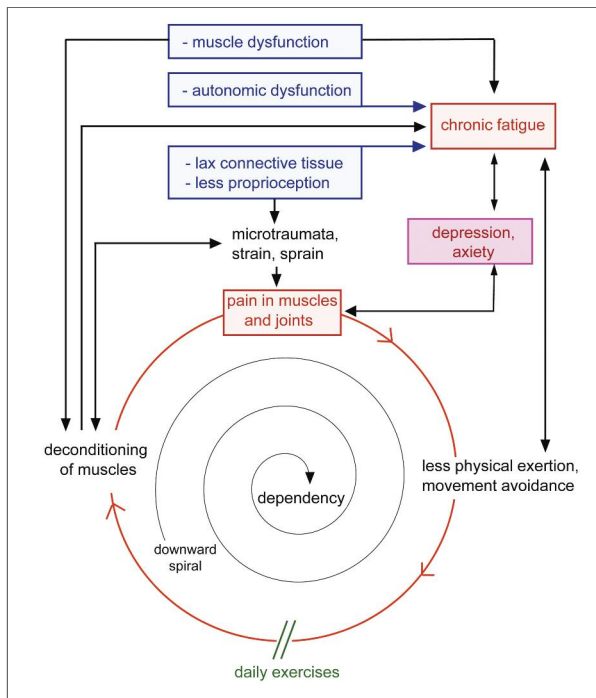


FIGURE 1. Vicious circle in generalized hypermobility of chronic pain and fatigue

Via several mechanisms, pain and chronic fatigue may ensue, leading to less physical exercise. This leads to physical deconditioning, associated with chronic pain and fatigue, and a vicious circle. The way to break this vicious circle and often downward spiral is to prevent or treat (further) physical deconditioning by daily physical training (exercises). Not all features have to be clearly present in all patients.

cle tension and coordination to maintain adequate joint position and body balance^{23,35,36} thus leading to fatigue. In addition, these patients often show muscle weakness²⁸, reduced exercise tolerance, physical deconditioning and pulmonary symptoms (see below)³⁷ commonly attributed to reduced exercise because of chronic pain (Figure 1). Finally, fatigue could be associated with depression and other psychological problems associated with generalized hypermobility^{34,38}. Most probably, fatigue is caused by a constellation of these factors, of which the individual impact will vary between patients.

Fatigue and generalized pain are paramount among the symptoms that establish a clinical similarity and diagnostic confusion between hypermobility syndromes and fibromyalgia^{13-16,39}. Some authors even argue whether fibromyalgia is merely a description of the symptoms of EDS or BMJS or a separate disease entity in these patients¹³⁻¹⁶.

AUTONOMIC DYSFUNCTION

Autonomic dysfunction comprises disturbances in a variety of functions dependent on the autonomic nervous system, leading for instance to postural hypotension and tachycardia, (pre)syncope and palpitations. Such symptoms have been reported in higher than expected frequency in patients with hypermobility syndromes.^{33,34} Lower urinary tract dysfunction associated with generalized hypermobility of joints may also be related to autonomic dysfunction, alongside laxity of the connective tissue of the pelvic floor and the sphincter^{40,41}. Gastro-intestinal disturbances common in hypermobility syndromes, such as gastro-esophageal reflux, constipation and irritable bowel syndrome or malabsorption, are more common in hypermobility syndromes as well and may share a similar pathophysiology⁴². The prevalence of both urinary and fecal incontinence has been described as significantly higher in women with hypermobility syndromes than in women without these conditions^{40,41,43-46}.

JOINT (SUB)LUXATION

Joint luxation or subluxation are not specific features of generalized hypermobility and hypermobility syndromes. Probably (sub)luxation reflects the severity of the joint laxity and impaired local muscle strength and coordination. If (sub)luxation occurs frequently in a specific joint, this often becomes less painful and sometimes (sub)luxation can be demonstrated by the patient on request.

OSTEOPOROSIS AND FRACTURES

In EDS and Marfan syndrome, a higher prevalence of low bone mineral density, osteopenia or osteoporosis are reported in most studies⁴⁷⁻⁵¹ but not all. In a study with 23 patients with EDS - hypermobility type and 23 matched controls, EDS subjects had a significantly lower bone mineral density at the femoral neck, but this difference disappeared after adjustment for body height, weight and physical activity levels⁵². Thus, reduced exercise or immobility induced by the hypermobility syndrome may be important in determining osteopenia, probably in association with the inherited structural deficit. Furthermore, an increased incidence of falls (and thus increased risk of fractures) has been reported in EDS - hypermobility type³⁶, due to impaired balance and muscle weakness. This might be at least partially preventable by appropriate exercise programs.

OSTEOARTHRITIS

A relationship between hypermobility syndromes and osteoarthritis would be expected especially as long-term complication in patients with frequent (sub)luxations. However, the literature data are equivocal: while some papers describe a relation between hypermobility and osteoarthritis^{53,54}, others even indicate an inverse relation⁵⁵⁻⁵⁷.

LIFE-THREATENING MANIFESTATIONS AND COMPLICATIONS

Some specific hypermobility syndromes may have life-threatening manifestations such as aneurisms and arterial ruptures in EDS vascular type, Marfan syndrome, Loeys-Dietz syndrome and the aneurism-osteoarthritis syndrome. Next to vascular complications, life-threatening ruptures of the bowel and of the pregnant uterus are also manifestations of EDS vascular type^{58,59}. Luckily, these manifestations or complications do not happen in the more frequently occurring hypermobility syndromes.

CLASSIFICATION INTO A SPECIFIC HYPERMOBILITY SYNDROME

For some of the hypermobility syndromes (e.g. EDS kyphoscoliotic type), the diagnosis can be made very early based on evident signs and symptoms. However, more frequently, the clinician will be faced with previously undiagnosed generalized hypermobility in a patient presenting with symptoms. In such cases, it most often concerns BJHS and EDS hypermobility type. More rarely, such patients may present with another syndrome, such as EDS classic type, Marfan syndrome (with mild phenotype) or EDS vascular type (still without clear vascular complications).

So, the first and most important step in eliciting such diagnosis is awareness of the broad spectrum of symptomatic hypermobility syndromes

Would classification of such cases into a specific syndrome be clinically important? And, if so, how could we best do that?

WHY CLASSIFY GENERALIZED HYPERMOBILITY?

It is important to identify and classify generalized hypermobility because some syndromes are associated with life-threatening risks outside the musculoskeletal system, as described above. Although these diseases cannot be cured and complications cannot be totally prevented, awareness and appropriate measures will diminish the risks of such events.

HOW TO GO ABOUT CLASSIFICATION?

Clinical diagnosis is, for most of the syndromes, based on clinical recognition of reported symptoms and signs at physical exam. For most syndromes, there are no (fully) discriminatory lab tests. Luckily, there are useful diagnostic tests for the majority of the rarer syndromes with life-threatening risks, like EDS vascular type, Marfan syndrome and Loeys-Dietz syndrome. However, the clinician must be aware that not all patients suffering from one of these syndromes have characteristic symptoms, which, in the absence of clinical awareness, will delay recognition often until the first severe vascular complication occurs. This is especially true in young adults. On the other hand, screening all patients with generalized hypermobility with genetic testing for these potentially life-threatening syndromes would not be a sensible option.

In practice, clinicians should first try to classify patients on the basis of the medical history (including the family) and the physical examination; if a specific syndrome is suspected, appropriate genetic testing may be considered, if available.

For nomenclature, it is recommended that specific hypermobility syndromes are only diagnosed or referred to if published classification criteria are satisfied. Patients who do not satisfy such classification criteria should be described simply as having *generalized hypermobility* or an *unclassified hypermobility syndrome*. Clinicians should refrain from using supposed synonyms for specific syndromes, such those employed for BJHS, composed of various combinations of terms 'benign', 'familial', 'generalized', 'articular', 'joint', 'hypermobility' and 'syndrome', leading to abbreviations like AHS, BFHS, BHS, BHJS, BJFHS, FAH, FGAH, FHS, JHS and HS. Such terms do not correspond to distinctive features and their use adds to confusion.

SPECIFIC HYPERMOBILITY SYNDROMES PRESENTING TO THE CLINICIAN

It can be challenging to classify a patient with generalized hypermobility. Note that specific hypermobility syndromes differ most in the non-musculoskeletal symptoms and signs. In fact, if such non-musculoskeletal symptoms and signs are absent or scarce, clinical classification is difficult given that the skeletal manifestations are very similar.

The clinician must be aware that frequently the signs and symptoms do not allow a clear discrimina-

tion. In the face of such uncertainty, it is important to remind what the key objective is: to make sure that syndromes with a high risk of life threatening, especially vascular complications, are not overlooked.

Pattern recognition and evaluation of discriminating features (Table V) help making the right diagnosis. Important clues come from the patient's history. For example, uncomplicated bowel and vascular surgery and uncomplicated vaginal delivery are arguments against EDS vascular type, even if they do not exclude this diagnosis completely^{60,61}. Specific discriminating signs or symptoms include the specific physique (phenotype) and lens dislocations in Marfan syndrome and the appearance of the skin^{62,63}, for instance in EDS. A family history of people dying relatively young of cardio-vascular complications, especially vascular ruptures, are clues for EDS vascular type, the related Loeys-Dietz syndrome, Marfan syndrome and the aneurism-osteoarthritis syndrome.

EDS-HYPERMOBILITY TYPE / BJHS

Diagnosis of these syndromes are based on clinical criteria, including generalized joint hypermobility, recurrent joint dislocations, chronic joint/limb pain, and skin involvement, although these features are neither fully discriminating nor pathognomonic. Muscle weakness, muscle pain, and muscle cramps, have also been suggested to be associated with EDS hypermobility type²⁸.

Symptoms of EDS hypermobility type (1997 Villefranche criteria¹) and of BJHS (1998 Brighton criteria⁶⁴) overlap considerably (Table IV). In both sets of criteria, general joint hypermobility is a key/major criterion, with some minor distinction regarding the required number of positive tests for qualifying positive for this criterion. In addition, recurrent joint (sub)luxation is an identical minor criterion for both BJHS and EDS hypermobility type. Other signs and symptoms serve as major criterion in one set and appear as minor sign in the other set of criteria. Specific laboratory (genetic) tests lack for both. So it comes as no surprise that there is discussion whether the EDS hypermobility type and the BJHS are two separate clinical syndromes or are in fact manifestations of one clinical condition^{65,66}. However, in a survey, most British rheumatologists considered EDS hypermobility type and BJHS to be two different entities, not one single syndrome⁶⁷. Also in a study on respiratory disorders, patients with EDS hypermobility type and BJHS were / could be discriminated³⁷, using the Villefranche

and Brighton criteria, respectively^{1,64}. The Brighton criteria seem to have an acceptable degree of reproducibility^{66,68}. One could discuss however which clinical purpose is served by the discrimination between EDS hypermobility type and BJHS as the therapeutic approach is the same.

Neither of these criteria sets include data on tenascin-X serum levels, which have been advocated to discriminate between the two diagnoses⁶⁹. Some studies describe reduced tenascin-X serum levels in 5-10% of EDS hypermobility type / BJHS patients, due to tenascin-X mutations,⁷⁰ which does not suggest any discrimination. Furthermore, the testing of tenascin-X is still challenging and not routinely available and discriminatory serum level cut-offs and test characteristics such as sensitivity, specificity and discriminating value are not yet known.

HYPERMOBILITY SYNDROMES A CLINICIAN SHOULD NOT OVERLOOK

These - mostly rare - hypermobility syndromes have potentially life threatening complications, such as rupture of arteries: EDS vascular type, the Loeys-Dietz syndrome^{71,72} Marfan syndrome and the aneurism-osteoarthritis syndrome.

EDS vascular type is associated with a bad prognosis: patients often die relatively young from rupture of arteries and/or hollow organs, such as intestines and uterus during pregnancy⁷³. The typical phenotype consists of thin and translucent skin, showing underlying veins, giving especially the hands an aged appearance ('acrogeria', see Figure 2) and nonspecific dimorphic features of the face. However, all these typi-



FIGURE 2. Acrogeria in a 32-year-old woman with EDS vascular type. The hand looks much older than the patient really is.

TABLE V. DISCRIMINATION OF GENERALIZED JOINT HYPERMOBILITY SYNDROMES*

Classification	Distinguishing feature
Idiopathic (end of distribution curve)**	none
Benign joint hypermobility syndrome**	none
Ehlers-Danlos types (table 5)**	lax skin; specific features of each type
Osteogenesis imperfecta	bone fragility
Loeys-Dietz syndrome	vascular complications
Stickler syndrome	eye problems, facial abnormalities
Marfan syndrome	skeletal habitus, lens dislocations, aortic arch dissections

*not comprehensive;

**possible overlap of generalized hypermobility as end of normal distribution curve of mobility of joints, benign joint hypermobility syndrome and Ehlers-Danlos hypermobility type

cal features may be absent.

The family history may reveal cases of ruptures of arteries and/or hollow organs, but the present patient could also be the only one in the family with EDS vascular type, due to a novel *point-mutation* in the COL3A1 gene. So, making a clinical diagnosis is not always easy; luckily there are genetic tests for this EDS-type (Table III).

Preventive measures are possible, including life style measures: avoiding sports with risk of trauma and with elevations of blood pressure, stop smoking, meticulous monitoring and control of blood pressure to low-normal values. In a study of 5-years duration, therapy with the beta-blocker celiprolol prevented major complications in patients with EDS vascular type, compared to EDS patients randomly assigned no drug therapy⁷⁴.

The phenotype of **Loeys–Dietz syndrome** overlaps with that of EDS vascular type (vascular ruptures) and of Marfan syndrome (aortic aneurysm / dissection and arachnodactyly). The syndrome is caused by *TGFBR1* or *TGFBR2* mutations, in the genes encoding for transforming growth factor b receptor type 1 or type 2, respectively. Transforming growth factor b is a cytokine that exerts diverse roles in cell proliferation and differentiation, apoptosis (programmed cell death), and extracellular matrix formation¹¹. Patients with *TGFBR1* or *TGFBR2* tend to have aortic dissections at smaller aortic-root diameters compared to patients with Marfan syndrome, but compared to patients with EDS vascular type, outcomes after aortic surgery are better^{72,75}.

The criteria for diagnosis of **Marfan syndrome** are presented in Table VI⁷⁶. They include involvement of the skeletal system (generalized hypermobility and marfanoid habitus as characterized by the major and

minor skeletal criteria of Table VI) the ocular system (lens dislocation), the cardiovascular system (aortic dissection) and the skin⁷⁷. However, among individual patients, considerable heterogeneity of phenotype, signs and symptoms is present¹¹.

Genetic testing of Marfan is directed at the many mutations in the *FBN1* gene, encoding the structural protein fibrillin-1. About 10% of patients with clinically typical Marfan syndrome have no mutation in this gene. In such cases, *TGFBR1* and *TGFBR2* mutations may be detected. To complicate things, *TGFBR1* and *TGFBR2* mutations are also found in Loeys–Dietz syndrome and may be detected in familial thoracic aortic aneurysms and dissections syndrome too⁷⁸. The angiotensin II receptor blocker losartan seems to inhibit progressive aortic root dilation in patients with Marfan syndrome^{12,79}. Stickler syndrome (hereditary progressive arthro-ophthalmopathy) may cause confusion with Marfan syndrome based on its possible clinical features hypermobility and skeletal abnormalities, such as pectus excavatum or carinatum and highly arched palate. However, skin laxity and vascular complications are not features of this syndrome (Table VII)^{80,81}. Although typical cases may be recognized at a young age, the diagnosis often is delayed by variability of the phenotype⁸². Genetic testing of the collagen type II gene locus *COL2A1* can confirm the clinical diagnosis⁸³.

The **aneurism-osteoarthritis syndrome** has features similar to Marfan syndrome, but lens dislocation does not occur and generalized hypermobility is less frequently present. Next to vascular complications these patients have osteoarthritis at a relatively young age. The specific genetic defect is a mutation of the *SMAD3* gene⁸⁴.

TABLE VI. GHENT 1996 DIAGNOSTIC CRITERIA FOR MARFAN SYNDROME⁷

System	Major Criteria	Minor Criteria
<i>Skeletal</i>	At least 4 of the following features: <ul style="list-style-type: none"> • Pectus carinatum • Pectus excavatum requiring surgery • Wrist and thumb signs • Upper-to-lower segment ratio <0.86 or span:height >1.05 • Scoliosis >20° or spondylolisthesis • Reduced elbow extension (<170°) • Pes planus • Acetabular protrusion 	Two of the major features, or 1 major feature and 2 of the following: <ul style="list-style-type: none"> • Joint hypermobility • Moderate pectus excavatum • High palate with dental crowding • Characteristic face (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)
<i>Ocular</i>	<ul style="list-style-type: none"> • Lens dislocation (ectopia lentis) 	<ul style="list-style-type: none"> • Flat cornea • Increased axial length of globe (causing myopia) • Hypoplastic iris or ciliary muscle (causing decreased miosis)
<i>Cardiovascular</i>	<ul style="list-style-type: none"> • Dilatation of aortic root involving the sinuses of Valsalva • Dissection of the ascending aorta 	<ul style="list-style-type: none"> • Mitral valve prolapse • Dilatation of the pulmonary artery and age <40 y • Calcified mitral annulus and age <40 y • Dilatation or dissection of the descending thoracic or abdominal aorta and age < 50 y
<i>Pulmonary</i>	None	<ul style="list-style-type: none"> • Spontaneous pneumothorax • Apical blebs on chest X-ray
<i>Skin</i>	None	<ul style="list-style-type: none"> • Striae atrophicae • Recurrent or incisional hernia
<i>Dura</i>	<ul style="list-style-type: none"> • Lumbosacral dural ectasia 	None
<i>Genetic</i>	<ul style="list-style-type: none"> • Family history: parent, child, or sibling meets these criteria independently • Test: fibrillin-1 mutation known to cause Marfan • Test: inheritance in the family of DNA marker haplotype linked to Marfan 	None

For all systems, having 1 of the features listed constitutes a major criterion or minor criterion except for the skeletal system, where >1 feature is needed.

The diagnosis of Marfan syndrome requires major criteria in 1 organ and minor criteria (involvement) of another when a positive family history or positive genetic testing (one of the two) is present. In the absence of a positive family history and positive genetic testing, meeting major criteria in at least 2 organ systems and minor criteria in at least a third organ system are required.

PRINCIPLES OF MANAGEMENT OF HYPERMOBILITY SYNDROMES

Although there are no randomized controlled studies regarding the effects of existing treatments for musculoskeletal problems in patients with symptomatic hypermobility, this does not mean that certain therapeutic strategies could not be helpful⁸⁵. They are mentio-

ned only briefly below.

- **Education** is the first step after the diagnosis. It should tackle the feelings of frustration with misunderstanding of the complaints by the medical profession and social entourage, often during many years⁸⁶; and the frustration about the absence of clear physical signs and laboratory abnormalities. It also comprises life style advices (e.g. on rest, sleep hygiene, activities,

TABLE VII. INVOLVED ORGAN SYSTEMS WITH THEIR MANIFESTATIONS IN STICKLER SYNDROME*^a**Orofacial abnormalities:**

- cleft palate (open cleft, submucous cleft, or bifid uvula), highly arched palate
- characteristic face (malar / midfacial hypoplasia, broad and/ or flat nasal bridge, micro / retrognathia)

Ocular abnormalities: vitreous and retinal degeneration (lattice degeneration, retinal hole, detachment or tear)

- Auditory abnormalities:
- high frequency (4–8 kHz) sensorineural hearing loss: at age <20: ≥ 20 dB, at age 20–40: ≥ 30 dB and at age >40: ≥ 40 dB
- hypermobile tympanic membranes

Skeletal abnormalities and symptoms:

- generalized joint hypermobility
- chronic musculoskeletal pain
- femoral head disorders (slipped epiphysis or Legg–Perthes-like disease)
- radiographically demonstrated osteoarthritis before age 40
- scoliosis, spondylolisthesis, or Scheuermann-like kyphotic deformity
- mild spondyloepiphyseal dysplasia
- pectus excavatum or carinatum

* This list is by no means exhaustive; there is variable intra- and interfamilial heterogeneity in the involvement of these organ systems

prevention of trauma), directions on self-help, redirecting false cognitions and other cognitive-behavioral strategies, coping, improving patient self-esteem and self-efficacy, genetic counseling.

• **Physical therapy and daily exercises at home** should be performed: toning exercises for stabilization of joints, exercises improving proprioception, exercises diminishing physical deconditioning (Figure 1) and improving posture. In patients with osteoarthritis of the hip or knee (without a hypermobility syndrome) exercise therapy has demonstrated efficacy in reducing pain and disability⁸⁷; in hypermobile children also a beneficial effect of physiotherapy on pain was found⁸⁸. It seems prudent to advice exercises to improve muscle strength and proprioception of joints, although in patients with hypermobility syndromes there is lack of data⁸⁹. The prospective study showing no relationship between joint hypermobility and injury in dan-

cers⁶, who often have a trained body, could also be an argument for exercises. There seems to be no contraindication against prudent stretching exercises, but long during hyperextension of joint, e.g. standing with hyperextended knees, should be avoided.

Modalities like heat or cold application, electrical stimulation to alleviate pain, acupuncture, acupressure, biofeedback, yoga and conscious relaxation are not evidence-based, but might have a beneficial effect on pain in some patients.

It seems prudent to advise weight-bearing exercises for the long bones and spine and an adequate intake of calcium and vitamin D in patients with a hypermobility syndrome, to prevent fractures.

• **Adaptations and assistive devices** (braces, grasps, waterbed, mattress, wheelchair, electric scooter), adapted shoes, adaptations to living and working environment could all have a place in the management strategy. Care should be put in avoiding that adaptations and assistive devices lead to less physical exercises or activities, as this could potentially be harmful by increasing physical deconditioning and ensuing complaints. However, adaptations and assistive devices may lead to increased activities and there can be medical and social reasons to prescribe them.

• **Drugs**, such as medications for pain, disturbed sleep, depression and fatigue could have a place in the management of selected patients with hypermobility syndromes. However, in chronic diseases, these drugs usually only have a mild, often temporarily symptomatic effect. Apart from treating hypertension, which is always necessary, in Marfan syndrome, losartan has a place and celiprolol in EDS vascular type, to diminish the risk of vascular complications.

• **Surgical procedures** on joints should be avoided, if possible. For example, in patients with hypermobility and repetitive luxation of the shoulder, surgery often is ineffective, according to clinical experience.

AREAS OF UNCERTAINTY

The exact incidence of most of the hypermobility syndromes is not known. Possibly specific (types of) hypermobility syndromes are genetically based on different genetic aberrations; several new types of EDS have been recognized on the basis of genetic defects over the past years. Although specific drugs have been shown beneficial in Marfan syndrome and EDS vascular type; it has not been investigated whether (other) antihypertensive medications would have a similar effect. Although scarce literature data indicate a benefi-

cial effect of physiotherapy and exercises, the real long-term effect is not known, nor the effects, pros and cons of specific physiotherapeutic modalities.

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