ARTICLE

Differential Diagnosis and Diagnostic Flow Chart of Joint Hypermobility Syndrome/Ehlers–Danlos Syndrome Hypermobility Type Compared to Other Heritable Connective Tissue Disorders

MARINA COLOMBI, CHIARA DORDONI, NICOLA CHIARELLI, AND MARCO RITELLI

Joint hypermobility syndrome/Ehlers–Danlos syndrome hypermobility type (JHS/EDS-HT) is an evolving and protean disorder mostly recognized by generalized joint hypermobility and without a defined molecular basis. JHS/EDS-HT also presents with other connective tissue features affecting a variety of structures and organs, such as skin, eye, bone, and internal organs. However, most of these signs are present in variable combinations and severity in many other heritable connective tissue disorders. Accordingly, JHS/EDS-HT is an "exclusion" diagnosis which needs the absence of any consistent feature indicative of other partially overlapping connective tissue disorders. While both Villefranche and Brighton criteria include such an exclusion as a mandatory item, a systematic approach for reaching a stringent clinical diagnosis of JHS/EDS-HT is still lacking. The absence of a consensus on the diagnostic approach to JHS/EDS-HT concerning its clinical boundaries with similar conditions contribute to limit our actual understanding of the pathologic and molecular bases of this disorder. In this review, we revise the differential diagnosis of JHS/EDS-HT with those heritable connective tissue disorders which show a significant overlap with the former and mostly include EDS classic, vascular and kyphoscoliotic types, *osteogenesis imperfecta*, Marfan syndrome, Loeys–Dietz syndrome, arterial tortuosity syndrome, and lateral meningocele syndrome. A diagnostic flow chart is also offered with the attempt to support the less experienced clinician in stringently recognizing JHS/EDS-HT and stimulate the debate in the scientific community for both management and research purposes.

KEY WORDS: joint hypermobility syndrome; Ehlers–Danlos syndrome hypermobility type; differential diagnosis; heritable connective tissue disorders; diagnostic flow chart

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INTRODUCTION

Joint Hypermobility Syndrome and Ehlers-Danlos Syndrome Hypermobility Type (JHS/EDS-HT)

Joint hypermobility syndrome (JHS) and Ehlers–Danlos syndrome hypermobility type (EDS-HT) (OMIM #130020) are two markedly overlapping heritable connective tissue disorders (HCTDs), which are recently considered as the same nosologic entity [Beighton et al., 1998; Grahame et al., 2000; Tinkle et al., 2009; Castori et al., 2014]. EDS-HT (estimated prevalence 1:5,000–15,000) reported in the last EDS classification, i.e., the Villefranche nosology (Table I), shows an autosomal dominant inheritance, and it is defined by the association of two major criteria, i.e., generalized joint hypermobility (JHM), and smooth, velvety, poorly hyperextensible skin. Recurring joint dislocations, chronic joint/limb pain, and positive family history are minor diagnostic criteria (Table I) [Beighton et al., 1998]. EDS-HT is the most common disorder belonging to the expanding group of EDS, and together with Marfan syndrome (MFS) is the most frequent HCTD known so far. Nevertheless, in contrast to the other EDS variants, its molecular basis remains unknown [Castori et al., 2014; Malfait and De Paepe, 2014]. JHS, originally considered a condition distinct from EDS-HT, is assessed by Brighton criteria [Grahame et al., 2000], which consider JHM and its complications (pain, dislocations) and other skin, ocular, soft tissue signs of connective tissue involvement (Table II). The further set of diagnostic criteria proposed by Levy [2004] includes additional features not previously considered, i.e., functional bowel disorders, neurally mediated hypotension or postural orthostatic tachycardia, high narrow palate and dental crowding. In the last years JHS/EDS-HT has emerged as a multisystemic disease associated with a wide inter- and intrafamilial variability with mucocutaneous [Castori, 2012 Castori et al., 2015], skeletal [Castori, 2012], cardiovascular [Camerota et al., 2014], gastrointestinal [Zarate et al., 2010; Danese et al., 2011], gynecological [Castori et al., 2012a], neurological [Voermans et al., 2009; Garcia Campayo et al., 2011; De Wandele et al., 2014], and psychiatric manifestations [Pasquini et al., 2014] (Table III).

Joint Hypermobility (JHM)

JHM is still the most clinically relevant feature of JHS/EDS-HT. It refers to the ability to actively and/or passively move the joints beyond normal limits [Beighton et al., 1973]. JHM may affect a few joints (i.e., monoarticular or localized JHM) or several joints in multiple body sites (i.e., generalized JHM). JHM can be directly assessed using the Beighton score (BS), a nine-point evaluation (Beighton et al., 1973; Fig. 1). In patients without JHM according to the BS, a 5-point questionnaire is available to investigate historical JHM [Grahame et al., 2000; Hakim and Grahame, 2003; Tinkle et al., 2009] (Table II). JHM is a sign, not a disease, and its occurrence varies by age, sex, and ethnicity. In fact, the majority of hypermobile individuals are asymptomatic, and loose joints are more common among females and children than males and older people [Beighton et al., 1973]; lastly, even some occupational and sport activities may naturally improve JHM [Castori, 2012]. In JHS/EDS-HT generalized JHM contributes to generate various orthopedic complications, which include increased tendency to recurrent generalized dislocations, widespread chronic pain, soft-tissue lesions (i.e., bursitis, tenosynovitis) and *pes planus* [Castori et al., 2010a; Castori, 2012].

JHS/EDS-HT Natural History

The natural history of JHS/EDS-HT is characterized by a progressive worsening of the phenotype, usually mild in the infancy and more severe in the adulthood [Castori et al., 2010a, 2013]. The existence of two distinct sets of diagnostic criteria for JHS/EDS-HT probably reflects the natural history within a single condition, which may have different clinical presentations at various ages [Tinkle et al., 2009; Castori et al., 2014]. Indeed, the diagnostic criteria for JHS/EDS-HT reported by the Villefranche nosology [Beighton et al., 1998] are adequate for children and young adults evaluation, whereas the Brighton criteria, considering the natural progressive loss of joint mobility by age, are more suitable to assess adults [Grahame et al., 2000; Tinkle et al., 2009; Castori, 2013a].

Diagnosis and Differential Diagnosis of JHS/EDS-HT

To date, the diagnosis of JHS/EDS-HT is clinical and based on the agreement of largely accepted diagnostic criteria together with the exclusion of other partially overlapping HCTDs. No instrumental, histopathologic/ultrastructural, and molecular finding is considered pathognomonic of this disorder. Assessment of JHS/EDS-HT lays on accurate clinical history taking and extensive physical examination, including dermatologic, oral cavity, orthopedic, and neurologic evaluations [Castori, 2013a].

The wide clinical variability of JHS/EDS-HT identifies a great number of partially overlapping acquired and genetic disorders showing the variable association of mucocutaneous fragility, JHM, chronic musculoskeletal pain, and fatigue. Among them, there are other HCTDs with JHM, the "battered child" syndrome, bleeding disorders, developmental coordination disorder, and various rheumatologic conditions with chronic musculoskeletal pain, such as ankylosing spondylitis, rheumatoid arthritis, and fibromyalgia. Some neurologic disorders, including multiple sclerosis, amyotrophic lateral sclerosis, hereditary and acquired sensory-motor and/or autonomic polyneuropathies, and chronic fatigue syndrome, as well as myopathies featuring JHM have to be considered [Castori, 2012, 2013a]. Among the various HCTDs sharing some musculoskeletal features with JHS/EDS-HT, there is the growing

TABLE I. The Villefranche Criteria for the Historical EDS Types [Beighton et al., 1998] and the Underlying Molecular Defect

EDS type	Major criteria	Minor criteria	Gene(s)
Classic	**Skin hyperextensibility**[a]	Smooth, velvety skin	*COL5A1*
AD	**Widened atrophic scars**	**Molluscoid pseudotumors**	*COL5A2*
OMIM #130000, #130010	JHM	Subcutaneous spheroids	
		Complications of JHM (e.g., sprains, dislocations/subluxations, *pes planus*)	
		Muscle hypotonia, delayed gross motor development	
		Easy bruising	
		Manifestations of tissue fragility (e.g., hiatal hernia, anal prolapse in childhood, cervical insufficiency)	
		Surgical complications (postoperative hernias)	
		Positive family history	
Hypermobility	Skin involvement (hyperextensibility and/or smooth, velvety skin)	Recurring joint dislocations	?
AD	Generalized JHM	**Chronic joint/limb pain**	
OMIM #130020		Positive family history	
Vascular	Thin, translucent skin	**Acrogeria**	*COL3A1*
AD	**Arterial/intestinal/uterine fragility or rupture**	Hypermobility of small joints	
OMIM #130050	**Extensive bruising**	Tendon and muscle rupture	
	Characteristic facial appearance	*Talipes equinovarus* (clubfoot)	
		Early-onset varicose veins	
		Arteriovenous, carotid-cavernous *sinus fistula*	
		Pneumothorax/pneumohemothorax	
		Gingival recession	
		Positive family history, **sudden death in (a) close relative(s)**	
Kyphoscoliotic	Generalized JHM	Tissue fragility, including atrophic scars	*PLOD1*
AR	Severe muscle hypotonia at birth	Easy bruising	
OMIM #225400	**Scoliosis at birth, progressive**	Arterial rupture	
	Scleral fragility and rupture of the ocular globe	*Marfanoid habitus*	
		Microcornea	
		Radiologically considerable osteopenia	
		Family history, i.e., affected sibs	
Arthrochalasia	Severe generalized JHM, with recurrent subluxations	Skin hyperextensibility	*COL1A1*
AD	**Congenital bilateral hip dislocation**	Tissue fragility, including atrophic scars	*COL1A2*
OMIM #130060		Easy bruising	
		Muscle hypotonia	
		Kyphoscoliosis	
		Radiologically mild osteopenia	

TABLE I. (*Continued*)

EDS type	Major criteria	Minor criteria	Gene(s)
Dermatosparaxis	**Severe skin fragility**	Soft, doughy skin texture	*ADAMTS2*
AR	**Sagging, redundant skin**	Easy bruising	
OMIM #225410		**Premature rupture of fetal membranes**	
		Large hernias (umbilical, inguinal)	

[a]Items in bold are distinguishing features of the particular EDS type.

group of the other EDSs, MFS, Loeys–Dietz syndrome (LDS), arterial tortuosity syndrome (ATS), milder forms of *osteogenesis imperfecta* (OI), and lateral meningocele syndrome (LMS) [Callewaert et al., 2008a,b; Castori et al., 2013b; Malfait and De Paepe, 2014; Van Dijk and Sillence, 2014; Van Laer et al., 2014]. The clinical overlap of JHS/EDS-HT with these HCTDs, its evolving and variable phenotype, and the absence of the causal gene(s) make the diagnostic process difficult. This difficulty is hampered in pediatric patients without a complete manifestation of the specific disorder by which they are affected [Tofts et al., 2009]. JHS/EDS-HT often becomes the "default" diagnosis either of a hypermobile child or an adult who does not meet the criteria for diagnosis of one of the other HCTDs. Therefore, the JHS/EDS-HT is probably a heterogeneous group and particularly in pediatric patients the evaluation of parents and relatives should be considered, as well as the opportunity of genetic testing for other HCTDs with known molecular basis, which might address, by exclusion or confirmation, a correct diagnosis. In this review, we will focus on the differential diagnosis of JHS/EDS-HT with the other EDS types and with HCTDs with JHM, cutaneous, skeletal, vascular, and internal organs overlapping manifestations and will delineate a flow chart for a clinical diagnostic approach to JHS/EDS-HT patients.

DIFFERENTIAL DIAGNOSIS WITH OTHER EDS TYPES INCLUDED IN THE VILLEFRANCHE NOSOLOGY

EDS needs to be considered when, in the absence of another explanation, one or more of the following manifestations occurs: (i) late walking with joint hypermobility, (ii) abnormal bruising and bleeding, (iii) tissue fragility, atrophic scarring or skin hyperextensibility, (iv) symptomatic joint hypermobility with or without dislocations, (v) unexplained vessel rupture or dissection, (vi) internal organ rupture [Sobey, 2014]. Although EDS variants show an extensive clinical overlap, the Villefranche nosology identifies distinctive features for the six historical forms, considered as major or minor clinical criteria for inclusion (Table I). The major specific criteria can be all present or not and their combination with minor features suggests the diagnosis in a large majority of the cases. For the recently characterized EDS forms (Table IV) established diagnostic criteria are not available, also due to the rarity of the patients. For all of the EDS variants the connective tissue signs are increasing as far as new patients are investigated and reported, and nowadays the clinical picture of EDSs is more puzzling than depicted by the Villefranche nosology. JHS/EDS-HT is a clear example of this expanding knowledge (Table III). Besides JHS/EDS-HT, the other more frequently observed EDS types are, in decreasing order, the classic, vascular, and kyphoscoliotic types. The arthrocalasia and the dermatosparaxis types are infrequently observed entities. Dermatosparaxis is clearly distinguishable from JHS/EDS-HT (Table I) and is not considered in the differential diagnosis.

EDS Classic Type

JHS/EDS-HT has a great clinical overlap with EDS classic type (cEDS) since they both share cutaneous and articular signs and their complications (Table I). However, the high skin hyperextensibility together with widened atrophic/papyraceous scars, and, more rarely, molluscoid pseudotumors, are more remarkable and distinctive of cEDS [Ritelli et al., 2013] (Table I). In fact, in JHS/EDS-HT skin is usually poorly hyperextensible and papyraceous scars and molluscoid pseudotumors are absent. Small atrophic scars are observed in 1/4 of JHS/EDS-HT cases and orthopedic post-surgical atrophic scars are also present in 1/4 of the subjects, generally adults [Castori et al., 2015]. In a few cases, cEDS and JHS/EDS-HT may share similar cutaneous presentations and cEDS patients without atrophic scars (5% of the cases), or with small atrophic scars [Ritelli et al., 2013], as well as JHS/EDS-HT patients with

TABLE II. Brighton Criteria for Assessing JHS and 5-Point Questionnaire for Historical JHM

Brighton criteria for JHS	5-point questionnaire for JHM
Major criteria	1. Could you ever place your hands flat on the floor without bending your knees?
Beighton score ≥4/9	2. Could you ever bend your thumb to touch your forearm?
Arthralgia for >3 months in >4 joints	3. As a child did you amuse your friends by contorting your body into strange shapes OR could you do the splits?
Minor criteria	4. As a child or teenager did your shoulder or kneecap dislocate on more than one occasion?
Beighton score 1–3	5. As a child or teenager did you consider yourself double-jointed?
Arthralgia in 1–3 joints	
History of joint dislocations	
Soft tissue lesions >3	
Marfan-like *habitus*	
Skin *striae*, hyperextensibility, or scarring	
Downslanting palpebral fissures, lid laxity, myopia	
History of varicose veins, hernia, visceral prolapse	
Agreement: both major, or 1 major and 2 minor, or 4 minor criteria. Criteria major 1 and minor 1 are mutually exclusive as/are major 2 and minor 2.	**Agreement:** affirmative answer for two or more questions.
Source: Grahame et al., [2000] and subsequent modifications (see, for example, Tinkle et al., [2009]).	**Source:** modified from Hakim and Grahame [2003].

marked hyperextensible skin are reported. In these patients, the careful investigation of affected family members, possibly showing cEDS-like scars, and the molecular analysis of the cEDS causal genes, i.e., *COL5A1* and *COL5A2,* allows for the distinction of cEDS from JHS/EDS-HT patients [Ritelli et al., 2013]. JHS/EDS-HT remains an exclusion diagnosis for the absence of known causal gene(s). Concerning articular involvement, cEDS patients suffer from chronic and/or generalized joint pain; however, in the majority of the cases it does not need chronic pharmacological treatment [Ritelli et al., 2013]. In cEDS and in the other EDS forms chronic pain might be underestimated. In a very few patients with hyperextensible skin, atrophic scarring, easy bruising, and JHM, propensity for arterial rupture at adult age is present [Malfait et al., 2007; Ritelli et al., 2013] (Table IV). These patients, defined as vascular-like cEDS individuals, typically carry arginine to cysteine substitution in the pro-α1(1) collagen chain.

EDS Vascular Type

JHS/EDS-HT is clearly distinguishable from the EDS vascular type (vEDS) (Table I) for the vascular, skin, and internal organs fragility, and for the characteristic facial appearance, i.e., triangular face with sunken and large eyes, thin lips and *philtrum*, small chin, and thin nose present in some patients. Generalized vascular fragility largely dominates the clinical picture of this life-threatening condition, indeed the majority of vEDS patients (~80% within 40 years) experienced a major vascular events (i.e., spontaneous aortic dissection or dissection of a previously aneurysmatic aorta), potentially resulting in sudden death. Hence, in adulthood vEDS patients commonly receive a diagnosis after referral to emergency surgeons for vascular dissection/rupture [Pepin et al., 2000; Oderich et al., 2005]. In JHS/EDS-HT aortic dissections are extremely rare, and aortic root ectasia is observed with an overall incidence of approximatively 12% without an increased risk of dissection [Atzinger et al., 2011]. In vEDS visceral rupture (i.e., bowel, lungs, liver, spleen, uterus during pregnancy, heart) may also occur for internal organs fragility [Drera et al., 2011; Murray et al., 2014]; in JHS/EDS-HT internal organs rupture is not reported, whereas visceroptosis due to ligaments hypoplasia and deterioration may be present (Table II) [Dordoni et al., 2013]. The fragility of the capillaries and of the perivascular connective tissues can lead to easy bruising with ecchymosis for minimal traumas both in vEDS and JHS/EDS-HT patients, though these features are more prominent in vEDS [De Paepe and Malfait, 2004]. In fact, in childhood vEDS patients are usually referred to pediatricians for the presence of frequent ecchymosis and "battered child" syndrome can be considered as differential. Concerning cutaneous signs, in vEDS skin is not hyperextensible but rather thin, transparent/translucent, sometimes showing a visible venous pattern over the chest, abdomen and extremities, and fragile with mild atrophic scarring. Acrogeria can be observed in patients harboring specific mutations in *COL3A1* [Drera et al., 2011]. JHM in vEDS generally involves small joints, but can be generalized in some patients. The few vEDS patients with generalized JHM and without major vascular events or internal organ rupture may partially overlap with the JHS/EDS-HT phenotype; in these cases, the presence of thin skin, visible venous network, acrogeria, vascular imaging diagnostic for arterial aneurysm, and positive family history for

TABLE III. Clinical spectrum of JHS/EDS-HT

System/apparatus	Clinical finding	Reference
Mucocutaneous	Mildly hyperextensible skin	Beighton et al., [1998]
	Velvety/silky/soft skin texture	Castori, [2012]
	Striae rubrae and/or *distensae* in young age	Castori, [2013]
	Small or post-surgical atrophic scars (non-papyraceous)	Castori et al., [2015]
	Keratosis pilaris	Wiesmann et al., [2014]
	Inguinal/umbilical/incisional hernia	
	Light *blue sclerae*	
	Gingival inflammation/recessions	
	Hypoplastic lingual *frenulum*	
	Easy bruising	
	Resistance to local anaesthetic drugs	
Osteoarticular	Generalized joint hypermobility	Beighton et al., [1998]
	Recurrent dislocations (mostly at hips, shoulders,	Levy, [2004]
	temporomandibular joint, fingers, and *vertebrae*)	Castori et al., [2010a]
	Recurrent soft-tissue lesions (bursitis, tendonitis,	
	synovitis, tenosynovitis, and fasciitis)	
	Temporomandibular joint dysfunction	
	Chronic /recurrent not inflammatory joint pain	
	Chronic generalized pain	
	Muscular/myofascialneuropathic/osteoarthritic	
	Early osteoarthritis	
Orthopedic	High arched/narrow palate	Beighton et al., [1998]
	Flat foot	Grahame et al., [2000]
	Not surgical *pectus excavatum*	Gulbahar et al., [2006]
	Mild scoliosis, dorsal hyperkyphosis, lumbar hyperlordosis	Castori, [2012]
	Genua, *halluces,* and *cubita valga*	
	Minor asymmetry at lower limbs and other body areas	
	Non-postmenopausal reduced bone mass	
	Marfanoid habitus (i.e., arm span/height ratio >1.03, arachnodactyly)	
Muscular	Hypotonia of mild degree	Castori, [2012]
	Recurrent myalgias and cramps	Voemans et al., [2009]
	Fibromyalgia	
	Myofascial pain	
	Involuntary muscle contractions	
	Reduced muscle power (rare)	
Gastrointestinal	Dysphagia and dysphonia	Castori et al., [2010]
	Gastroesophageal reflux	Danese et al., [2011]
	Hiatal hernia	Dordoni et al., [2013]
	Chronic/recurrent gastritis	Zarate et al., [2010]
	Delayed gastric empty	
	Defecatory dysfunction	
	Delayed small bowel and colonic transit	
	Unexplained abdominal pain	
	Various food intolerances	
	Visceroptosis	
Cardiovascular	Valvular regurgitation with mild hemodynamic involvement	Atzinger et al., [2011]
	Mitral valve prolapse/insufficiency	Camerota et al., [2014]
	Varicose veins	De Wandele et al., [2014]
	Low progressive aortic root dilatation	
	Raynaud's phenomenon/acrocyanosis/*livedo reticularis*	
Uro-gynecological	Meno/metrorrhagias	Castori et al., [2012a]
	Disabling dysmenorrhea	

(*Continued*)

TABLE III. (*Continued*)

System/apparatus	Clinical finding	Reference
	Pelvic prolapse	
	Dyspareunia	
	Urinary stress incontinence	
Neuropsychiatric	Chronic fatigue (syndrome)	Rombaut et al., [2010]
	Sleep disturbances	Castori, [2012]
	Impaired memory and concentration	Granata et al., [2013]
	Headache and migraine	De Wandele et al., [2014]
	Recurrent paresthesias	Neilson et al., [2014]
	Cardiovascular dysautonomia (e.g., postural orthostatic tachycardia syndrome, neuromediated hypontension)	Pasquini et al., [2014]
	Somatosensory/central sensitization	
	Clumsiness	
	Anxiety, panic, and fears	
	Depression	
	Obsessive-compulsive disorder	
Ocular	Myopia and/or strabismus	Castori, [2012]
	Palpebral ptosis	

arterial dissection in young age can support the diagnosis. Molecular analysis of *COL3A1* can confirm or exclude this diagnosis.

EDS Kyphoscoliotic Type

JHS/EDS-HT is distinguishable from the kyphoscoliotic type of EDS (kEDS) (Table I) for the recessive inheritance, the presence of early onset progressive kyphoscoliosis, neonatal thoracic scoliosis, and severe muscular hypotonia with delayed gross motor development, osteopenia, microcornea, and in some patients scleral fragility with risk for rupture of the globe, and occurrence of life-threatening rupture of medium-sized arteries [Rohrbach et al., 2011]. Features common to kEDS and JHS/EDS-HT are mainly cutaneous, i.e., fragile, hyperextensible, and bruisable skin with atrophic scarring, articular, i.e., generalized JHM, and skeletal. The diagnosis of kEDS relies on the demonstration of an increased ratio of deoxypyridinoline to pyridinoline crosslinks in urine, caused by deficient activity of lysyl hydroxylase 1, the enzyme encoded by *PLOD1*. Alternatively, an assay of lysyl hydroxylase enzyme activity in skin fibroblasts is diagnostic. Mutations in *PLOD1* are causative [Rohrbach et al., 2011].

EDS Arthrochalasia Type

The arthrochalasia type of EDS (aEDS) is characterized by severe generalized JHM and bilateral congenital hip dislocation (CHD) (Table I). Generalized JHM is shared as a major feature with JHS/EDS-HT; CHD can be also observed in JHS/EDS-HT patients, but it is not a major sign and in most cases is unilateral (our unpublished data). Other signs distinguishing aEDS from JHS/EDS-HT are marked hypotonia at birth, short stature, and wormian bones [Klaassens et al., 2012]. Hence, bilateral CHD in patients with extreme JHM and significant hypotonia at birth suggests aEDS and molecular testing for a specific set of *COL1A1* and *COL1A2* mutations, involving their exons 6 splice junctions, can confirm the diagnosis. In patients without a causal mutation clinical diagnosis of JHS/EDS-HT has to be considered searching for cardiovascular, gastrointestinal, gynecological, and neurological signs (Table III), which at the moment are not reported in aEDS patients.

DIFFERENTIAL DIAGNOSIS WITH RARE EDS TYPES

Concerning the rare EDS forms not included in the Villefranche nosology, detailed phenotypes are reported for the few patients so far characterized (Table IV). The major cause of the historical EDSs appears to be impaired biosynthesis and enzymatic modification of the three main fibrillar collagens, but EDSs are also associated with proteoglycan abnormalities (the progeroid and the musculocontractural types of EDS), as well as with alteration of an endoplasmic reticulum folding protein (EDS with progressive kyphoscoliosis, myopathy and hearing loss), of transcription factors (Brittle cornea type 1 and 2), and of a zinc transporter (spondylocheirodysplastic EDS). This heterogeneity of causes involving several systems leads to the variety of distinguishable phenotypes reported in Table IV. On the other hand, since the genes involved in this growing number of EDS types encode for components or regulators of the connective tissue extracellular matrix, common features are present in the different variants which have to be considered in differential diagnosis with JHS/EDS-HT, especially for their articular and cutaneous signs (Table IV) [Malfait and De Paepe, 2014; Miyake et al., 2014; Sobey, 2014]. In particular, JHS/EDS-HT shows a marked overlap with a small subset of patients with homozygous /compound heterozygous *TNXB* mutations (TNX-deficient

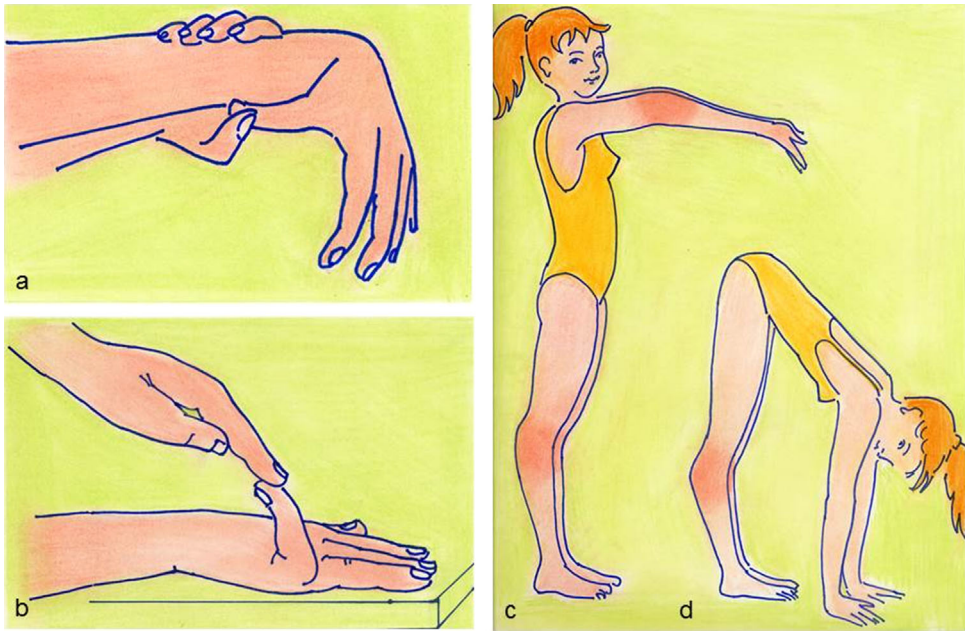

Figure 1. Assessment of joint hypermobility with the Beighton score: (a) passive dorsiflexion of the fifth metacarpophalangeal joint to ≥90°, (b) opposition of the thumb to the volar aspect of the ipsilateral forearm, (c) hyperextension of the elbow to ≥10°, and hyperextension of the knee to ≥10°, d) placement of hands flat on the floor without bending the knees (Figure drawn by L. Manenti). The Beighton score is incorporated into the diagnostic criteria for EDSs, MFS, LDS, ATS, and OI.

patients), but also with the heterozygous carriers of mutations leading to *TNXB* haploinsufficiency, including a recurrent 30 kb deletion involving *TNXB* and *CYP21A2* [Schalkwijk et al., 2001; Zweers et al., 2003], therefore suggesting that the EDS phenotype associated with TNX-deficiency is a dose-dependent phenomenon. The patients with the 30 kb deletion in homozygosity [Burch et al., 1997], or in compound heterozygosity with a second *CYP21A2* mutation [Mercke et al., 2013], also present with congenital adrenal hyperplasia (CAH). In patients with CAH and TNXB haploinsufficiency (CAH-X syndrome), mainly due to the recurrent 30 kb deletion, JHM is the predominant clinical feature, in addition to variable findings including joint dislocations, chronic joint pain, and soft tissue lesions [Mercke et al., 2013]. Therefore, in patients with JHM and CAH the presence of the 30 kb *TNXB* deletion should be investigated. Patients with complete TNX-deficiency show a marked cEDS overlapping phenotype without atrophic scarring [Schalkwijk et al., 2001], whereas TNXB haploinsufficiency, without concomitant CAH, results in JHS/EDS-HT phenotype [Zweers et al., 2003; Mercke et al., 2013]. Recently, it is emerging that TNX-deficient patients also suffer from myopathy, generalized muscle weakness, and possible distal contractures in adult age [Pénisson-Besnier et al., 2013; Voermans et al., 2014]. Myopathic pattern at electromyography is observed also in some JHS/EDS-HT patients who complain of neuromuscular symptoms, i.e., muscle cramps and myalgia, and in other EDS variants, i.e., musculocontractural type 1 and type 2 EDS, progressive kyphoscoliosis, myopathy and hearing loss EDS, and progeroid type 1 and type 2 EDS (Tables I, III, and IV) [Voermans et al., 2009; Baumann et al., 2012]. Since JHM secondary to muscle hypotonia in combination with cutaneous features is also observed in Ullrich congenital muscular dystrophy, and in the allelic Bethlem myopathy [Voermans et al., 2008], also these myopathies have to be considered in the differential with JHS/EDS-HT, especially in pediatric patients.

The periodontitis EDS type is distinguished for the severe periodontal disease characterized by irreversible destruction of the periodontal tissues (periodontal ligament, alveolar bone, and connective tissue) leading to premature loss of teeth, associated with JHM and atrophic scars [Reinstein et al., 2013]. For this heterogeneous disorder the molecular basis is still unknown. Periodontal disease is common also in JHS/EDS-HT patients, but true parodontopathy with early tooth loss is rarely observed, whereas gingival fragility and inflammation causing bleeding, retraction, and impaired oral cleansiness are common [Castori, 2012]. Otherwise, gingival mucosal fragility is not a specific sign of JHS/EDS-HT, as it is found in about 74% of the EDS population without any significant difference between the most prevalent subtypes, i.e., cEDS, JHS/EDS-HT, and vEDS [De Coster et al., 2005]. Instead, dentin defects, i.e., abnormal pulp shape and pulp stones, appear to be more specific of cEDS or vEDS, and it was never described in JHS/EDS-HT [De Coster et al., 2005; Ferrè et al., 2012]. Gingival regression was considered a minor Villefranche criterion for vEDS; however, recent evidences suggested that it is inappropriate for its low frequency among vEDS patients [Ferrè et al., 2012].

TABLE IV. EDS Forms Not Included in the Villefranche Nosology with the Clinical Features and the Involved Genes

EDS variant	Feature	Gene(s)	Reference
Classic vascular-like AD	Hyperextensible skin Atrophic scarring Easy bruising JHM **Propensity for arterial rupture at adult age**[a]	*COL1A1*	Malfait et al., [2007] Ritelli et al., [2013]
Cardiac valvular AR OMIM #225320	**Severe mitral valve regurgitation/insufficiency** Arrhythmia, atrial fibrillation and septal defect, left *ventriculum* enlargement JHM Skin hyperextensibility	*COL1A2*	Schwarze et al., [2004]
Tenascin-X deficiency AR OMIM #606408	Marked skin hyperextensibility Normal scarring Generalized JHM Severe easy bruising	*TNXB*	Schalkwijk et al., [2001] Pénisson-Besnier et al., [2014] Voermans et al., [2014]
EDS/OI overlap AD	**Short stature** *Blue sclerae* **Mild signs of bone fragility** **Osteopenia** Infrequent fractures Generalized JHM Skin hyperextensibility Atrophic/hypertrophic scars Easy bruising Signs of vascular fragility Valvular regurgitation	*COL1A1* *COL1A2*	Malfait and De Paepe, [2014]
Periodontitis AD OMIM #130080	**Gingival recessions** **Periodontitis** **Premature loss of permanent teeth** **Alveolar bone resorption by the IIIrd decade** Atrophic scars JHM Umbilical hernia Arachnodactyly	Locus heterogeneity Unknown genes	Reinstein et al., [2013b]
Musculocontractural type 1/ D4ST1 deficiency AR OMIM #601776	**Congenital contractures of thumbs and fingers** Craniofacial dysmorphisms *Blue sclerae* **Microcornea** Clubfoot Arachnodactyly Severe kyphoscoliosis Muscle hypotonia JHM Hyperextensible skin Atrophic scars Easy bruising Wrinkled palms	*CHST14*	Malfait et al., [2010]
Musculocontractural	**Joint dislocations and deformity**	*DSE*	Müller et

TABLE IV. (*Continued*)

EDS variant	Feature	Gene(s)	Reference
type 2	Hyperextensible fragile skin		al., [2013]
AR	Atrophic scarring		
OMIM #615539	Easy bruising		
	Muscle hypoplasia		
	Gross motor development delay		
	Facial dysmorphisms		
	Arachnodactyly		
	Adducted thumbs		
	Clubfoot		
	Inguinal hernia		
	Generalized mild cerebral atrophy		
With progressive kyphoscoliosis, myopathy and hearing loss	Severe hypotonia and weakness at birth	*FKBP14*	Baumann et al.,
	Hyperextensible skin		[2012]
	JHM		
	Severe progressive scoliosis		
AR	**Sensorineural hearing impairment**		
OMIM #614557	**Myopathy**		
	Vascular dissection		
Brittle cornea syndrome type 1	*Blue sclerae*	*ZNF469*	Burkitt Wright et
	Corneal rupture		al., [2013]
AR	***Keratoconus/keratoglobus***		
OMIM #229200	Skin hyperextensibility		
	JHM		
Brittle cornea syndrome type 2	**Corneal rupture**	*PRDM5*	Burkitt Wright et
	Microcornea		al., [2011,
AR	***Cornea plana***		2013]
OMIM #614170	***Keratoconus/keratoglobus***		
	Myopia		
	Hyperextensible skin		
	Easy bruising		
	JHM (localized)		
	Pectus excavatum		
	Scoliosis		
	Mitral valve prolapse		
	Hearing loss (conductive and sensorineural deafness)		
Spondylocheirodysplasia EDS-like	Short stature	*SLC39A13*	Giunta et al., [2008]
	Protuberant eyes		
AR	*Blue sclerae*		
OMIM #612350	Hyperextensible skin		
	Easy bruising		
	JHM		
	Hands with wrinkled palms		
	Tenar muscles atrophy		
	Tapering fingers		
	Spondyloepiphyseal dysplasia		
Progeroid type 1	**Aged appearance**	*B4GALT7*	Guo et al., [2013]
AR	**Short stature**		
OMIM #130070	**Forearm bones and elbow anomalies, radioulnar synostoses**		
	Bowing of the extremities		
	Facial dysmorphisms		
	Hyperextensible skin		

TABLE IV. (*Continued*)

EDS variant	Feature	Gene(s)	Reference
	Atrophic/papyraceous scars		
	JHM		
	Pes planus		
	Developmental delay		
	Muscle hypotonia		
Progeroid type 2/ Spondyloepimetaphyseal dysplasia with joint laxity type 1 AR OMIM #615349 OMIM #271640	Aged appearance	*B3GALT6*	Nakajima et al., [2013] Malfait et al., [2013] Ritelli et al., [2015]
	Developmental delay		
	Disproportionate short stature		
	Craniofacial disproportion		
	Generalized severe osteopenia		
	Defective wound healing		
	Hyperextensible skin		
	JHM		
	Muscle hypotonia		
	Spondyloepimetaphyseal dysplasia		

AD, autosomal dominant; AR, autosomal recessive.
[a]Items in bold are distinguishing features of the particular EDS type.

In the rare spondylocheirodysplasia-like and progeroid type 1 and 2 EDS variants, JHM and hyperextensible skin are associated with skeletal dysplasia, including moderate to severe disproportionate short stature, pathognomonic bone deformities, and/or severe kyphoscoliosis with platyspondyly. Since short stature and evident bone deformities are absent in JHS-EDS-HT, differential diagnosis between these conditions is straightforward; skeletal and spine radiography can classify bone and vertebral alterations, reinforcing clinical diagnosis of these EDS types with skeletal dysplasia. In JHS/EDS-HT skeletal alterations include moderate scoliosis and platyspondyly, leg length discrepancy, *genua valga*, *hallux valgus*, as well as early onset osteopenia [Castori, 2012; our unpublished data]. These skeletal signs, observed also in other EDS, f.e., cEDS [Ritelli et al., 2013], are not specific of JHS/EDS-HT and are not useful in differential diagnosis.

JHM with recurrent dislocations and soft/fragile/hyperextensible skin are also found in a disorder with combined connective tissue and neurological features, i.e., the periventricular heterotopia EDS variant (OMIM #300537), in addition to bilateral nodular heterotopia on brain MRI, aortic dilatation and dissection in early adulthood, excessive bleeding and bruisability, and skeletal abnormalities. This X-linked disorder, due to dominant mutations in filamin A gene (*FLNA*), is lethal in males and presents with epilepsy in heterozygous females. Since some patients can primarily present with JHM, screening for cardiovascular manifestations should be offered when there are associated seizures or an X-linked pattern of inheritance [Reinstein et al., 2013].

DIFFERENTIAL DIAGNOSIS WITH OTHER HCTDs

Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) comprises a heterogeneous group of diseases characterized by susceptibility to bone fractures with variable severity. The last available classification identifies OI with mild to moderate severity, i.e., non-deforming OI with *blue sclerae* (type I), common variable OI with normal *sclerae* (type IV), and OI with calcification and interosseous membranes (type V); severe progressively deforming OI (type III), and perinatally lethal OI (type II) [Van Dijk and Sillence, 2014].

JHM is reported in non-deforming OI with *blue sclerae* (OI type I, OMIM #166200); these patients are distinguishable for the presence of *blue sclerae* and wormian bones; *dentinogenesis imperfecta* (i.e., opalescent dentine) and sensorineural deafness may be present in a subset of the patients [Steiner et al., 2005]. Reduction in the synthesis of type I procollagen and the presence of mutations in *COL1A1* confirm the diagnosis of OI type I with normal teeth, whereas *COL1A2* mutations are present in OI type I patients with opalescent dentine. The other OI subtypes are not considered in the differential with JHS/EDS-HT for: (i) the perinatal lethality (type II), (ii) the presence of respiratory and swallowing problems in newborns, and multiple long-bone fractures at birth with progressive deformity (type III), (iii) short stature, basilar impression, and long bones bowing (type IV), (iv) calcification of the interosseous membranes and/or hypertrophic *callus* (type V) [Van Dijk and Sillence, 2014]. Occasionally, patients are encountered who

display a phenotype that combines clinical manifestations of both OI and EDS. These OI/EDS patients present relevant bone fragility with repeated fractures and overt *blue sclerae* together with marked joint hypermobility and instability, skin hyperextensibility and/or translucency, and signs of peripheral vascular fragility (Table IV). The majority of OI/EDS patients harbor a dominant mutation in the most N-terminal part of the type I collagen helical region in either the α1- or α2-chain, which affects to some extent processing of the N-propeptide [Malfait and De Paepe, 2014].

Marfan Syndrome

Marfan syndrome (MFS) (OMIM #154700) is a relatively common autosomal dominant multisystem HCTD that exhibits marked inter- and intrafamilial variability with predominant manifestations in the cardiovascular, skeletal, and ocular systems; additionally, the skin, fascia, lung, skeletal muscle, and adipose tissue may be involved [Pyeritz, 2000]. The clinical diagnosis is based on the revised Ghent nosology, which can include the presence of a mutation in *FBN1* encoding fibrillin 1 [Loeys et al., 2010]. When moderate JHM is associated with a *marfanoid habitus* (tall and slender build, arachnodactyly and/or true dolichostenomelia, i.e., arm span/height ratio ≥1.05) coupled with a history of *ectopia lentis* and/or aortic dilatation or aneurysm, MFS should be strongly suspected. In about one-third of JHS/EDS-HT patients a *marfanoid habitus* is recognizable and includes arachnodactyly, dolichostenomelia with an arm span:height ratio ≥1.03 (which is significantly different from the cut-off of the revised Ghent criteria which is 1.05), long hands and feet, increased skin stretches in young age, JHM and characteristic changes in the *pectus* physiology [Hakim and Grahame, 2003; Grahame and Hakim, 2013]. Aortic root ectasia, another distinctive feature of MFS, is reported in a subset (about 12%) of JHS/EDS-HT patients [Atzinger et al., 2011]. However, aortic root ectasia in JHS-EDS-HT young patients, unlike in MFS, does not show any progression in adulthood [Castori, 2012; Atzinger et al., 2011]. JHS-EDS-HT patients presenting with *marfanoid habitus* and aortic root ectasia are comparable but distinguishable from MFS patients for *ectopia lentis*, which is not reported in JHS/EDS-HT. In most cases of MFS, JHM spares the elbows and *pectus* deformities are common and generally more impressive than in JHS/EDS-HT.

MASS syndrome (Mitral valve, Aorta, Skeleton, and Skin syndrome; OMIM #604308) is a MFS-related phenotype sharing skeletal features, i.e., scoliosis, *marfanoid habitus*, and JHM, and cutaneous signs, i.e., *striae rubrae/distensae*, and is distinguishable for mitral valve prolapse (MVP), aortic root ectasia without progression to aneurysm or dissection, and absence of *ectopia lentis* [Glesby and Pyeritz, 1989; Dietz et al., 1993]. JHS/EDS-HT patients with a *marfanoid habitus* may show a great overlap with MASS phenotype when MVP is present. The rate of MVP in JHS/EDS-HT is not well delineated. Contrasting data exist as in some reports its incidence does not seem significantly higher than in controls [Atzinger et al., 2011], while others found a clearly increase in rate [Camerota et al., 2014]. Hence, in the small subset of JHS/EDS-HT patients with *marfanoid habitus* and MVP *FBN1* molecular analysis should be considered.

Loeys–Dietz Syndrome

Loeys–Dietz syndrome (LDS1–4, OMIM #609192, #610168, #613795, #614816) is an autosomal dominant aortic aneurysm syndrome with multisystem involvement and inter- and intrafamilial variability. LDS is characterized by a clinical triad including hypertelorism, bifid uvula or cleft palate, and aortic aneurysm with arterial tortuosity. Natural history is significant for life-threatening aortic dissection that occur at smaller aortic diameter and younger age compared to MFS. Aortic aneurysms can be detected throughout the whole arterial tree. Furthermore, a widespread involvement of different organ systems was also recognized and include craniofacial (e.g., craniosynostosis), musculoskeletal (JHM, *marfanoid habitus* with arachnodactyly, dolichostenomelia, *pectus* deformities and joint contractures), integumental (e.g. skin hyperextensibility, *dural ectasia*), and ocular findings (e.g., *strabismus*) [Loeys et al., 2005; Loeys and Dietz, 2008]. A group of LDS patients, previously defined as LDSII, presents with severe vascular involvement together with thin, translucent skin, atrophic scars, and marked easy bruising, and without craniosynostosis and/or *marfanoid habitus,* thus resembling vEDS [Loeys and Dietz, 2008; Drera et al., 2008, 2009; Fattori et al., 2012]. LDS3 can show osteoarthritis in young age [Van de Laar et al., 2011; Regalado et al., 2011; Wischmeijer et al., 2013]. LDS4 presents a lower rate of life-threatening aortic dissection compared to the other LDS types, a high rate of MVP, JHM, and skeletal signs common to MFS [Lindsay et al., 2012; Boileau et al., 2012; Ritelli et al., 2014a]. LDS clinically overlaps with MFS also for aortic root aneurysm and for skeletal deformities and can be distinguished for the absence of *ectopia lentis* and for the presence of craniosynostosis, hypertelorism, bifid uvula, severe vascular involvement, and early osteoarthritis. JHS/EDS-HT with *marfanoid habitus* may partially overlap with LDS with mild vascular involvement and without craniosynostosis as LDS4; in these cases familial investigation and arterial evaluation are mandatory [Ritelli et al., 2014a]. Molecular analysis of the genes involved in LDS, i.e., *TGFBR1*, *TGFBR2*, *SMAD3*, and *TGFB2,* encoding for components of the transforming growth factor beta (TGFβ) signaling pathway, conclude the diagnosis of LDS.

Recently also *TGFB3* mutations were reported to be associated with abnormal development of several mesenchymal-derived tissues, including muscle and craniopalatofacial structures, accompanied by low muscle mass, growth retardation, distal arthrogryposis, and other secondary changes (Rienhoff syndrome). The syndrome

shares some clinical features with the MFS and LDS, including arachnodactyly, *pectus excavatum*, *pes planus*, and hyperextensible large joints, as well as hypertelorism and bifid uvula without evidence of vascular disease [Rienhoff et al., 2013; Matyas et al., 2014; Rienhoff, 2014] and is distinguishable from JHS/EDS-HT for the absence of mucocutaneous features, and the presence of growth retardation, hypertelorism, distal arthrogryposis, and positive *TGFB3* genetic testing.

Arterial Tortuosity Syndrome

Arterial tortuosity syndrome (ATS, OMIM #208050) is a rare, autosomal recessive HCTD chiefly characterized by tortuosity and elongation of the large- and medium-sized arteries and a propensity towards aneurysm formation and vascular dissection. Additional cardiovascular features include aberrant origin of aortic branches, arterial and pulmonary valve stenosis, and vasomotor instability. ATS also shares with other HCTDs soft/velvety/hyperextensible skin, *cutis laxa*, mildly dysmorphic facial features (i.e., elongated face, hypertelorism, cleft palate and/or bifid uvula, and micro/retrognathia), *keratoconus*, abdominal hernias, joint hypermobility and instability, and other skeletal anomalies. Systemic symptoms and sudden death due to acute respiratory insufficiency and/or cardiac failure can occur in the pediatric age [Callewaert et al., 2008b; Ritelli et al., 2014b]. ATS is caused by mutations in *SLC2A10* [Coucke et al., 2006; Ritelli et al., 2014b], encoding for the facilitative glucose transporter 10, GLUT10. For patients without cardiovascular complications, EDS can be suspected and particularly JHS/EDS-HT for the cutaneous, articular and skeletal signs; in these cases, cardiovascular evaluation and *SLC2A10* molecular analysis allow the distinction between these disorders [Castori et al., 2012b].

Lateral Meningocele Syndrome

Lateral meningocele syndrome (LMS), a rare HCTD described in 14 patients belonging to nine families, is characterized by widespread spinal lateral meningoceles (meningeal *diverticula*) protruding through the intervertebral spaces, in association with facial dysmorphisms and variable signs of connective tissue involvement, including JHM, present in about 74% of reported patients, and chronic musculoskeletal pain, found in about 64,3% of the cases [Castori et al., 2013b]. Cutaneous signs, i.e., hyperextensible and soft skin, are rarely disclosed (21% of the patients). Multiple meningeal *diverticula* have never been reported in JHS/EDS-HT patients or in cEDS, kEDS, MFS, and LDS, hence the presence of this clinical sign can distinguish LMS.

DIAGNOSTIC FLOW CHART OF JHS/EDS-HT

When a patient presents with JHM and variable cutaneous signs, including soft, velvety, thin, hyperextensible skin, *striae rubra*e or *distensae*, and abnormal scarring, a clinical evaluation is mandatory in order to identify other possible signs of connective tissue fragility, and his/her family history must be investigated. In particular, clinical signs indicative of the different forms of EDS and of the partly overlapped HCTDs (MFS, LDS, ATS, OI, and LMS) should be sought. A synthetic flow chart with the main clinical signs present in JHS/EDS-HT and in the most frequently observed EDSs and HCTDs that have to be considered in the differential with JHS/EDS-HT is reported in Figure 2. This flow chart will address the diagnostic suspicion of physicians or specialists in one of the different clinical fields of interest for JHS/EDS-HT. In a specialized center, the careful clinical evaluation and the assessment of the reported findings is sufficient to confirm the JHS/EDS-HT diagnosis in the majority of the cases (about 90% - Colombi, unpublished data). Only in pediatric patients and in patients without a complete or with a borderline phenotype the diagnosis is doubtful and requires a second evaluation in older age or targeted molecular testing for the exclusion of overlapping disorders. When specific signs of the different EDSs or HCTDs are found, the initial diagnosis is addressed accordingly.

When the presence of other EDSs, OI, MFS, LDS, ATS, or LMS is suspected, additional investigations for the assessment of vascular, skeletal, ophthalmologic, and bone health should be performed. In particular, when the suspicion of a vascular disorder (i.e., vEDS, LDS, ATS) persists, extensive vascular imaging (i.e., whole body angio-MRI, or brain angio-MRI plus thoracic and abdominal angio-CT, or heart, abdominal aorta, epiaortic and limb vessels Doppler ultrasound) is mandatory. When MFS is suspected heart ultrasound for MVP and aortic root ectasia, ocular evaluation for *ectopia lentis* and/or myopia, and spine MRI for dural ectasia must be performed. In patients with an OI type I resembling phenotype, bone densitometry for early osteoporosis/osteopenia, skull radiography for wormian bones, orthodontic evaluation for *dentinogenesis imperfecta* are required. In LMS patients spine MRI is needed.

In EDSs ultrastructural examination of the skin usually reveals abnormalities of collagen fibrils which include irregular, disrupted fibrils ("collagen flowers"), and variability within their diameter. However, these abnormalities are common to several EDS variants and usually not specific enough to discriminate between individual EDS types, with the exception of the pathognomonic hieroglyphic fibers observed in the dermatosparaxis type of EDS [Malfait and De Paepe, 2014]. At the moment, ultrastructural abnormalities are only occasionally identified in JHS/EDS-HT and no finding is specific of this condition. Therefore, skin biopsy ultrastructure is not included in the standard diagnostic schedule of JHS/EDS-HT [Castori, 2013]. This is also the case of biochemical analyses, none is available for JHS/EDS-HT, whereas some have been developed for other EDSs. In particular, the biochemical evaluation of urinary pyridinoline confirms the kEDS diagnosis and distinguishes this form from EDS with progressive kyphoscoliosis, myopathy

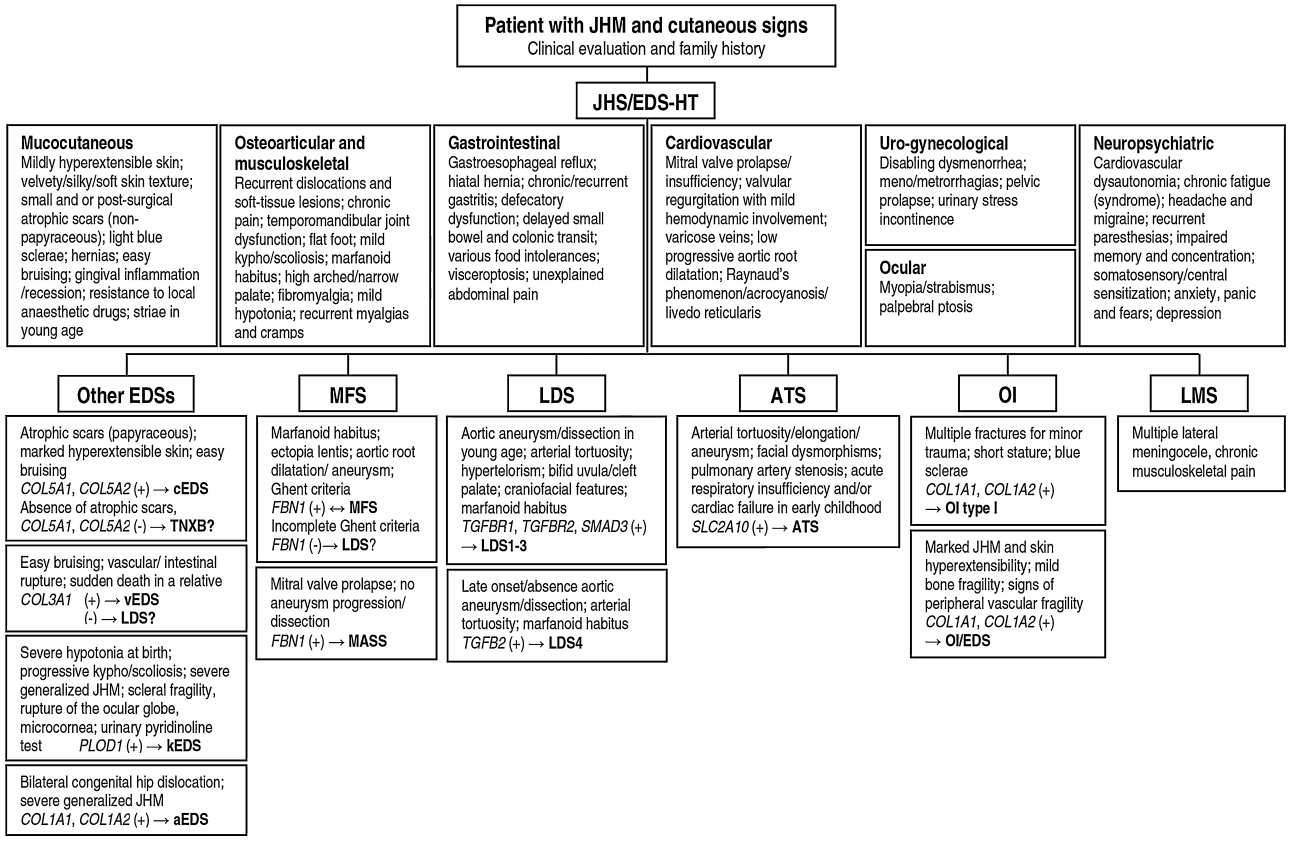

Figure 2. Diagnostic flow chart for a patient presenting with JHM and cutaneous features which considers JHS/EDS-HT, the most frequently observed EDSs, MFS, LDS, ATS, OI, and LMS.

and hearing loss and from JHS/EDS-HT overlapping phenotypes.

Genetic testing is available for all of the genes involved in the so far defined EDS types, except JHS/EDS-HT and the periodontitis type, and for the other HCTDs, except LMS, and mutation detection can be performed on genomic DNA obtained from peripheral blood sample either by Sanger sequencing or by targeting panel-based NGS. The molecular evaluation of *COL5A1* and *COL5A2* allows for the distinction of cEDS patients without scarring and generalized JHM from JHS/EDS-HT; and if no mutations in these genes are detected *TNXB* analysis could be performed. *COL1A1* and *COL1A2* analysis permits the distinction of OI type I and OI/EDS from the overlapping JHS/EDS-HT phenotypes. Molecular testing for the *COL3A1*, *FBN1, TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, and *SLC2A10* genes confirms/excludes the diagnosis of the HCTDs with prominent vascular involvement. Rapid detection of such rarer HCTDs is crucial for prognosis establishment due to their high risk of vascular accidents, a complication never reported in JHS/EDS-HT. Exclusion of other overlapping HCTDs is a crucial step in borderline patients to confirm the clinical diagnosis of JHS/EDS-HT, allowing the multidisciplinary management of these patients, which covers pharmacologic, physical therapy, surgical, and nutraceutical aspects, as well as general lifestyle recommendations.

CONCLUSIONS

Diagnosis of JHS/EDS-HT can be difficult due to the intrafamilial and interfamilial variability, the evolving presentation, the multisystem involvement, the unknown molecular basis, and the overlap with a wide spectrum of other disorders either inherited or acquired. Careful clinical evaluation of JHS/EDS-HT patients and their families for all the known manifestations of this disorder, and the application of the diagnostic flow chart with the overlapping HCTDs, should facilitate a correct diagnosis to the different specialists following these patients, including clinical geneticists, rheumatologists, dermatologists, orthopedists, ophthalmologists, cardiologists, gynecologists/ obstetricians, neurologists, and clinical psychologists. All these patients should refer to centers specialized in the diagnosis of these disorders also offering genetic testing to be diagnosed in a short time and to receive an appropriate management. For JHS/EDS-HT the future challenge will be the definition of its molecular basis; the knowledge of the causal gene(s) will give a powerful diagnostic tool and likely open novel therapeutic perspectives.

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