

# Natural History and Manifestations of the Hypermobility Type Ehlers–Danlos Syndrome: A Pilot Study on 21 Patients

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Hypermobility type Ehlers–Danlos syndrome (HT-EDS) is a relatively frequent, although commonly misdiagnosed variant of Ehlers–Danlos syndrome, mainly characterized by marked joint instability and mild cutaneous involvement. Chronic pain, asthenia, and gastrointestinal and pelvic dysfunction are characteristic additional manifestations. We report on 21 HT-EDS patients selected from a group of 40 subjects with suspected mild hereditary connective tissue disorder. General, mucocutaneous, musculoskeletal, cardiovascular, neurologic, gastrointestinal, urogynecological, and ear–nose–throat abnormalities are investigated systematically and tabulated. Six distinct clinical presentations of HT-EDS are outlined, whose tabulation is a mnemonic for the practicing clinical geneticist in an attempt to diagnose this condition accurately. With detailed clinical records and phenotype comparison among patients of different ages, the natural history of the disorder is defined. Three phases (namely, hypermobility, pain, and stiffness) are delineated based on distinguishing manifestations. A constellation of additional, apparently uncommon abnormalities is also identified, including dolichocolon, dysphonia, and Arnold–Chiari type I malformation. Their further investigation may contribute to an understanding of the pathogenesis of the protean manifestations of HT-EDS, and a more effective approach to the evaluation and management of affected individuals. © 2010 Wiley-Liss, Inc.

**Key words:** evolution; extra-articular; joint hypermobility; pain; presentation

## INTRODUCTION

Ehlers–Danlos syndrome (EDS) comprises a clinically variable and genetically heterogeneous group of inherited connective tissue disorders mainly characterized by skin hyperextensibility, joint hypermobility, and vascular and internal organ fragility [Callewaert et al., 2008]. The overall incidence of this condition has been estimated at approximately 1:5000 [Steinmann et al., 2002]. According to the most recent classification, six major forms

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exist, while other variants are considered rare [Beighton et al., 1998]. The clinical variability of each EDS subtype is extremely wide and the diagnosis is not always straightforward even for the experienced clinician. Misdiagnosis or lack of diagnosis represents a major burden for patients with EDS. In fact, a recent survey by the European Organization for Rare Diseases (EURORDIS) has demonstrated that among patients belonging to 16 major rare diseases, those affected with EDS have the longest delay in diagnosis and request consultation of up to 20 specialists before obtaining the correct diagnosis [Kole and Faurisson, 2009]. This has severe consequences on the quality of life of the patients [Castori et al., 2009], usually in term of excessive financial and time expense, superfluous investigations, wrong therapies, delay of appropriate treatments, and preventable worsening of the disease state.

Among the different forms of EDS, the hypermobility type (HT-EDS) is the most difficult to diagnose. This condition is an autosomal dominant trait and is more common in females. The HT-EDS represents a clinical continuum with the so-called (benign) joint hypermobility syndrome (JHS) [Grahame, 1999; Tinkle et al.,

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2009]. There is also a significant overlap with other forms of EDS, Stickler syndrome, osteogenesis imperfecta, and various fibrillinopathies [Grahame, 2000]. Given the lack of any skin, skeletal, ocular, or internal organ key anomaly, the phenotype of HT-EDS is limited to ligamentous laxity and minor and unspecific cutaneous defects [Hakim and Grahame, 2003]. Although recent papers pointed out an unexpected broadening of the phenotype [Hakim and Grahame, 2003], very little attention has been paid in the clinical genetics literature for the elaboration of evaluation strategies for properly diagnosing and counseling these patients.

Here, we report our experience on 21 patients with HT-EDS. Accurate phenotype study allowed us to further delineate the natural history and the clinical complexity of this condition.

## PATIENTS AND METHODS

From January 2007 to June 2009, patients were selected at the general clinical genetics outpatient service of the Medical Genetics Unit of the San Camillo-Hospital in Rome. Patients were referred for evaluation from different specialists, including rheumatologists, orthopedists, physiatrists, cardiologists, dermatologists, and pediatricians, for a suspected heritable connective tissue disorder. After a first examination, all patients were re-evaluated in order to identify those with a firm diagnosis of HT-EDS. The diagnosis was established when patients met both the Villefranche and Brighton criteria, for the HT-EDS and JHS, respectively [Beighton et al., 1998; Grahame et al., 2000], and other connective tissue and muscle disorders as well as developmental delay were excluded. Given the well-known overlap between HT-EDS and the mild (type II) classic EDS, we excluded from the study all patients with atrophic and/or hemosiderotic scars, molluscoid pseudotumors, or subcutaneous spheroids.

In selected patients, family, pregnancy/delivery, developmental and clinical history was systematically investigated and recorded by using a standardized questionnaire. Particular attention was posed on the presence of precipitous/preterm delivery, congenital dislocations, failure to thrive (i.e., reduced weight gain due to overt feeding problems), motor delay, frequency and location of subsequent joint dislocations, chronic articular and muscle pain, additional articular complications, easy bruising, gingival fragility (i.e., presence of multiple episodes of unexplained gingival hemorrhages or frequent toothbrush-induced hemorrhages), gingival retractions/parodontitis, recurrent caries, peripheral vascular disease, need for surgery and related complications, chronic asthenia, recurrent headaches, memory problems, anxiety and depression, gastrointestinal involvement (i.e., chronic gastritis, gastroesophageal reflux, recurrent abdominal pain, constipation, diarrhea and hemorrhoids), uterine, rectal and vesical prolapses, urinary incontinence (i.e., loss of urine occurring during physical activity) and sexual discomfort (especially in women), dysphonia, hearing impairment, and additional relatives with joint instability/hypermobility/chronic pain. We paid particular attention to the development of the phenotype, by requesting details on the progression of articular involvement over years. No specific scales were used for evaluating memory disturbances, anxiety and depression, but these traits were considered present when the patients themselves clearly stated to experience these problems.

Physical examination included a complete anthropometric and clinical evaluation. Body mass index (BMI) was also calculated. Joint mobility was assessed using the Beighton score. Accordingly, joint hypermobility was fixed with a score of 5/9 or greater. One point was scored for any of the following: (a) passive apposition of the thumb to the flexor aspect of the forearm (one point for each hand), (b) passive dorsiflexion of the 5th digit beyond 90° (one point for each hand), (c) hyperextension of the elbow beyond 10° (one point for each arm), (d) hyperextension of the knees beyond 10° (one point for each leg), (e) forward flexion of the trunk with the knees extended and the palms resting flat on the floor [Beighton et al., 1973]. Cutaneous laxity was assessed stretching the skin at the dorsal aspect of the IV metacarpal and of the forearm and was arbitrarily considered present for an extension of more than 10 mm in both sites. Pressure-induced (piezogenic) papules were recognized as small subcutaneous fat herniations through the dermis visible at heels, plantar arches, and volar aspect of wrists. All available patients underwent heart ultrasonography and, when possible, pulmonary function tests. Additional investigations performed elsewhere were also recorded. In specific cases, the exclusion of an inflammatory/infectious/autoimmune arthritis needed additional investigations, including complete blood cell count, erythrocyte sedimentation rate, rheumatoid factor, antinuclear antibody tests, serum complement, and immunoglobulin levels.

## RESULTS

From a total of 40 patients with mild features of heritable connective tissue disorder, we identified 21 (52.5%) subjects from 18 pedigrees with a confirmed diagnosis of HT-EDS. The remaining patients had Stickler syndrome, other forms of Ehlers–Danlos (commonly, the classic type) and too mild manifestations of unclassified joint hypermobility/connective tissue laxity. Age at diagnosis ranged from 8 to 58 years, with a mean of 34.8 years. Eighteen (85.7%) patients were female and three (14.3%) male. Of the 18 index cases, 7 (38.9%) had a family history of the condition. General, mucocutaneous, musculoskeletal, neurological, cardiovascular, gastrointestinal, urogynaecological, and ear-nose-throat findings are listed in Tables I and II. Other findings are listed in Table III.

### General Manifestations

Patients with HT-EDS were usually born without congenital dislocations (95.2%). Pregnancy of affected women and of unaffected mothers of affected children were uneventful, except for preterm and/or precipitous delivery occurring in approximately 1/3–1/4 of the cases (28.6%). No *peri- or post-partum* hemorrhage, or uterine rupture was registered. In one out of the four cases of uterine/vesical/rectal prolapse this complication arose as a late consequence of pregnancy (see below). In the first months/years of life, a relatively common complication (28.6%) was failure to thrive probably secondary to transient hypotonia manifesting with impairment of sucking and swallowing. Cognitive and motor development was normal in most patients. Marked joint instability caused delayed attainment of motor milestones in a single subject (4.8%). Although no patient displayed a true Marfanoid habitus (upper limb span-height ratio >1.03; upper-lower body segment

TABLE I. Mucocutaneous and Musculoskeletal Manifestations

Manifestations	Patients																					Total (%)
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Patient no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Sex	F	F	F	F	F	F	M	M	F	F	F	F	M	F	F	F	F	F	F	F	F	18F/3M
Age at diagnosis	49	39	58	57	25	41	53	15	25	36	8	45	26	41	13	38	36	32	34	14	45	n.a.
General																						
Precipitous/Preterm delivery	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-	+	+	+	+	-	-	6/21 (28.6)
Congenital dislocations	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	1/21 (4.8)
Failure to thrive	+	+	-	-	+	+	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-	6/21 (28.6)
Delayed motor development	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1/21 (4.8)
Mucocutaneous																						
Velvety/smooth skin	+	+	+	+	-	+	+	+	+	-	+	+	+	+	-	+	+	+	-	+	+	17/21 (80.9)
Hyperextensible skin	+	-	+	-	-	-	+	+	-	-	+	-	+	-	+	-	-	-	-	-	-	7/21 (33.3)
Skin fragility	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	+	-	-	-	-	2/21 (9.5)
Easy bruising	+	+	-	-	-	-	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	15/21 (71.4)
Piezogenic papules	+	+	-	+	-	+	+	+	-	n.a.	-	n.a.	-	+	-	+	+	+	-	+	+	12/19 (63.2)
Keratosis pilaris	-	-	-	-	-	-	+	+	-	-	-	-	+	+	-	-	+	-	+	-	-	6/21 (28.6)
Raynaud/Acrocyanosis	-	+	-	-	+	-	+	+	-	-	-	+	+	-	-	-	-	+	-	+	-	8/21 (38.1)
Gingival fragility	+	-	+	-	+	-	-	-	-	+	+	+	+	+	-	-	-	+	-	+	+	11/21 (52.4)
Recurrent caries	+	-	-	+	-	+	+	-	-	-	+	+	+	+	-	+	-	+	+	-	+	12/21 (57.1)
Musculoskeletal																						
Infancy/childhood joint hypermobility	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21/21 (100)
Residual joint hypermobility	+	+	+	-	+	+	-	+	+	+	n.a.	-	-	-	+	-	+	-	-	+	+	13/20 (65)
Articular dislocations	+	+	+	+	+	+	-	-	+	-	+	+	+	+	+	+	+	+	+	+	+	18/21 (85.7)
Ankle	+	+	+	+	+	+	-	-	-	-	+	+	-	+	-	+	+	+	+	-	+	14/21 (66.7)
Knee/patella	+	-	+	-	-	+	-	-	-	-	-	-	-	+	+	-	-	-	-	-	+	6/21 (28.6)
Hip	-	-	-	-	-	+	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	2/21 (9.5)
Fingers	-	-	+	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	3/21 (14.3)
Wrist	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	1/21 (4.8)
Elbow	+	-	+	-	-	-	-	-	-	-	+	+	-	-	-	+	-	-	-	-	-	5/21 (23.8)
Shoulder	-	-	+	-	-	+	-	-	-	-	-	+	-	-	-	+	-	+	-	-	-	5/21 (23.8)
Rib	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1/21 (4.8)
Temporomandibular	+	+	+	-	+	+	-	-	+	-	-	+	-	+	-	-	-	+	+	+	+	12/21 (57.1)
Ligament ruptures	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	3/21 (14.3)
Joint effusions	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2/21 (9.5)
Rec/chronic back pain	+	+	+	+	+	+	-	+	-	+	-	+	+	+	-	+	+	+	+	+	+	17/21 (80.9)
Rec/chronic myalgias	+	+	+	+	+	-	-	-	+	-	+	+	+	+	+	+	+	+	-	+	+	16/21 (76.2)
Rec/chronic arthralgias	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20/21 (95.2)

F, female; M, male; n.a., not available; Rec, recurrent.

ratio <0.89), 13 out of 21 subjects (61.9%) were ectomorph (slim and slender habitus with body mass index <19 [Maddan et al., 2008]).

## Mucocutaneous Manifestations

In our patients, the cutaneous phenotype of HT-EDS consisted of the triad of velvety/smooth skin (80.9%), easy bruising (71.4%), and pressure-induced papules (63.2%) (Fig. 1a,b; see also the clinical video clip). Capillary fragility was particularly evident at the anterior aspect of the legs below the knees (Fig. 1a). Skin hyperextensibility was rarer (33.3%) and always mild (Fig. 1c), while skin fragility was unusual (9.5%). Additional common

cutaneous findings included Raynaud phenomenon/acrocyanosis (38.1%) and keratosis pilaris (28.6%) (Fig. 1d). One patient (no. 17) had a small spontaneous herniation of subcutaneous fat with hypotrophy of the overlying skin at the lateral aspect of the right arm (Fig. 2a). Based on clinical records, this lesion arose at the site of an inflammatory papule caused very probably by an insect sting. Gingival fragility with recurrent toothbrush-induced or, more rarely, spontaneous hemorrhages (52.4%) and recurrent caries (57.1%) were reported consistently. Gingival retractions and alveolar bone reabsorption with secondary tooth loss (parodontitis) were registered in three patients (no.s 7, 12, and 21; Fig. 2b). In addition to HT-EDS, one patient (no. 18) also showed multiple painful lipomas (Dercum disease), requiring multiple operations.

**TABLE II. General, Neurological, Cardiovascular, Gastrointestinal, Urogynecological and Ear–Nose–Throat Findings**

Characteristic	Patients																					Total (%)
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Patient no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Sex	F	F	F	F	F	F	M	M	F	F	F	F	M	F	F	F	F	F	F	F	F	18F/3M
Age at diagnosis	49	39	58	57	25	41	53	15	25	36	8	45	26	41	13	38	36	32	34	14	45	n.a.
<b>Neurological</b>																						
Monolateral eyelid ptosis	+	-	+	-	+	+	-	+	-	-	-	+	-	-	-	-	+	+	-	-	8/21 (38.1)	
Chronic asthenia/fatigue	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	-	+	18/21 (85.7)
Recurrent headaches	+	+	+	+	-	+	+	+	+	-	+	+	+	-	-	-	+	+	+	-	+	15/21 (71.4)
Memory disturbances	+	+	+	+	-	n.a.	+	+	-	-	-	+	+	+	-	+	-	-	+	-	+	12/20 (60.0)
Anxiety/depression	+	+	+	+	-	+	+	+	+	+	-	+	-	+	-	-	+	-	-	-	+	13/21 (61.9)
<b>Cardiovascular</b>																						
Cardiac valve disease <sup>a</sup>	+	+	+	+	+	+	-	-	+	+	n.a.	n.a.	+	+	+	+	+	+	-	+	+	16/19 (84.2)
Respiratory insufficiency	+	+	+	n.a.	-	+	n.a.	n.a.	+	-	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	+	n.a.	n.a.	n.a.	+	7/9 (77.8)
Varicous veins/hemorrhoids	-	-	+	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	+	-	+	5/21 (23.8)
<b>Gastrointestinal</b>																						
Dyspepsia/chronic gastritis	+	+	+	-	+	+	-	+	-	+	-	+	+	-	-	+	+	+	-	+	+	14/21 (66.7)
Gastroesophageal reflux	-	+	-	-	+	+	-	+	-	+	+	-	-	+	-	+	+	+	+	-	+	12/21 (57.1)
Recurrent abdominal pain	-	+	+	-	+	+	-	+	-	+	+	+	-	-	-	+	+	+	-	+	+	13/21 (61.9)
Constipation/diarrhea	+	+	+	+	+	+	-	+	-	+	+	+	-	-	-	-	+	+	+	-	+	7/21 (33.3)
Umbilical hernia	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	1/21 (4.8)
<b>Urogynecological</b>																						
Prolapses	-	+	-	-	-	-	-	-	-	+	-	+	-	-	-	-	-	-	-	-	+	4/21 (19.0)
Stress incontinence	+	+	-	+	+	+	-	-	-	+	-	+	-	-	-	-	-	-	-	-	+	8/21 (38.1)
Dyspareunia	n.a.	n.a.	+	+	n.a.	n.a.	n.a.	n.a.	-	-	n.a.	n.a.	n.a.	-	n.a.	+	-	-	-	n.a.	-	3/10 (30)
<b>Ear-throat-nose</b>																						
Dysphonia	+	+	+	+	-	-	-	-	-	+	+	-	-	+	-	-	-	+	-	-	-	8/21 (38.1)
Conductive hearing loss	+	-	+	-	-	+	-	-	-	-	-	-	-	+	-	-	-	+	-	-	-	5/21 (23.8)

F, female; M, male; n.a., not available.  
<sup>a</sup>see text (Results) for more details.

### Musculoskeletal Findings

Infancy/childhood joint hypermobility was constant in our patients (100%). Its presence was evaluated on the basis of clinical examination (in young patients) or by a history for joint instability, congenital contorsionism, and joint laxity leading to an aptitude for specific sports such as gymnastics, ballet, and athletics. At the time

of examination, joint hypermobility was present in no more than two-third (66.7%) of patients (Fig. 1e–i). This discrepancy was probably due to progressive articular stiffness. Overall, recurrent joint dislocations were common (85.7%). Ankles (66.7%) and temporomandibular joint (57.1%) were the most commonly affected, followed by knees (28.6%), elbows (23.8%), shoulders (23.8%), and fingers (14.3%). Ribs (4.8%), wrists (4.8%), and hips (9.5%) were involved infrequently. Ligament rupture (14.3%) and joint effusions (9.5%) were rare complications. All but one patient (95.2%) complained of some form of recurrent/chronic arthralgias, myalgias, or back pain, the first being the most common.

**TABLE III. Other Findings**

- Post-surgical keloids (two patients)
- Resistance to local anesthesia (three patients)
- Post-surgical hernias (one patient)
- Post-inflammatory subcutaneous fat herniation (one patient)
- Multiple painful lipomas (one patient)
- Periodontitis (three patients)
- Arnold–Chiari malformation (one patient)
- Carotid tortuosity (one patient)
- Long colon (three patients)
- Colonic diverticula (one patient)
- Bladder diverticula (one patient)
- Severe myopia (one patient)

### Neurological Changes

Deep tendon reflexes, muscle tone, coordination, and walking were unremarkable in all patients. There were no focal deficits. Eyelid ptosis with or without blepharoclonus was observed in 38.1% of cases. Chronic asthenia, fatigue (85.7%), and recurrent headaches (60.0%) were a major complaint of these patients. Minor memory disturbances (60.0%) and anxiety/depression (61.9%) were also frequent. In one woman with severe recurrent headaches (no. 6), brain magnetic resonance imaging showed Arnold–Chiari malformation type I (Fig. 2c).



**FIG. 1.** Main manifestations of Ehlers–Danlos syndrome hypermobility type. Cutaneous findings [a–d]: easy bruising [a], pressure-induced papules [b; see also the clinical video clip], skin hyperextensibility [c], and Raynaud phenomenon [d]. Joint hypermobility [e–i]: hyperextension of the thumb in passive apposition to the flexor aspect of the forearm [e], hyperextension of the elbow [f] and knee [g] beyond  $10^\circ$ , forward flexion of the trunk with the knees extended and the palms resting flat on the floor [h], and hyperextension of the metacarpophalangeal joint of the V finger in passive dorsiflexion beyond  $90^\circ$  [i]. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

## Cardiovascular Abnormalities

Cardiovascular involvement was always mild with minimal clinical consequences. Cardiac valve disease, reported in 84.2% patients, usually involved the mitral and/or tricuspid valves. Other valves were only rarely affected. In most patients, heart ultrasound anomalies were trivial, without a clinical impact, as expected in the general population. In fact, ultrasonographic evidence of regurgitation was noted in 4 of 19 (21%) patients only. Aortic root diameter was within normal limits (i.e., 40 mm for males and 36 mm for females) in 20 patients. One 57-year-old woman (no. 4; 4.8%) showed slightly dilatation (38 mm) of the sinuses of Valsalva. Pulmonary function tests were not performed in all. However, seven of nine investigated patients (77.8%) had restrictive or mixed restrictive/obstructive mild respiratory insufficiency. Most of them manifested resting or activity-induced dyspnea. Considering the mean age at diagnosis of our patients, varicose veins and hemorrhoids were relatively uncommon (23.8%). One patient (no. 3) had asymptomatic tortuous carotids.

## Gastrointestinal Problems

Eighteen of 21 (85.7%) complained of chronic gastrointestinal discomfort. Recurrent/chronic dyspepsia/gastritis (66.7%), gastroesophageal reflux (57.1%), and manifestations of irritable bowel disease, including recurrent unexplained abdominal pain (61.9%) and constipation/diarrhea (33.3%), were reported. Abdominal hernias were rare (4.8%). Due to recurrent abdominal pain, three

patients (nos. 6, 10, and 12) underwent double contrast colon study which revealed dolichocolon (Fig. 2d). One patient (no. 1) had colonic diverticula (Fig. 2e).

## Urogynecological Features

Uterine/vesical/rectal prolapses were relatively rare (19.0%). However, they always manifested at a young age and represented a major problem for the affected individuals. Stress urinary incontinence was reported in 38.1% cases (all females). Three of 10 sexually active women (30%) complained of dyspareunia, most probably secondary to reduced vaginal secretion, as documented by gynecological evaluation. One patient (no. 1) had multiple bladder diverticula.

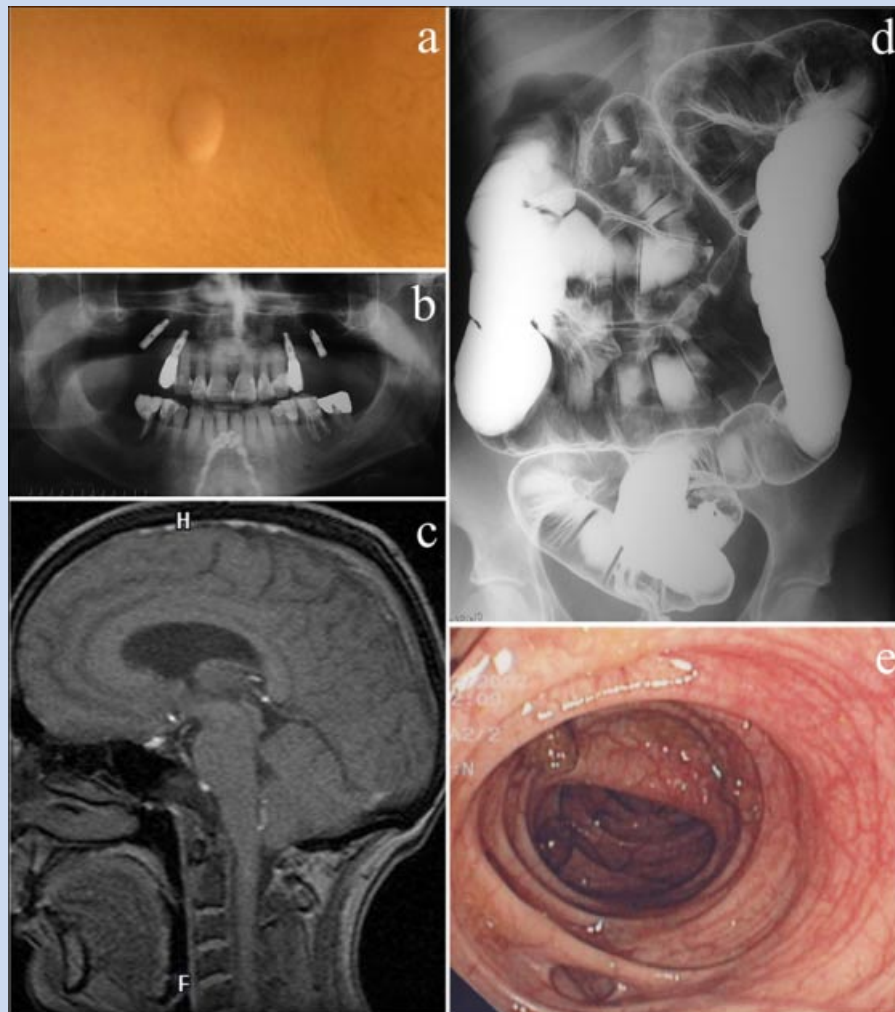
## Ear-Nose-Throat Changes

Dysphonia was relatively common in HT-EDS (38.1%). In patients who underwent further investigations, fibroscopy always demonstrated incoordination and/or hypotonia of the vocal cords. Hearing impairment was reported in five patients (23.8%). It was of mild degree, never requiring hearing aids.

## Surgical Complications

Overall, surgical complications were rare in our patients. The most common surgical procedure was tooth extraction for caries. Other operations were for multiple lipomas (one patient), lengthening of





**FIG. 2.** Rare findings of Ehlers–Danlos syndrome hypermobility type: post-inflammatory subcutaneous fat herniation (a), severe parodontitis with resorption of the alveolar bone (b), Arnold–Chiari malformation (c), dolicolon (d), and multiple colonic diverticula (e).

the Achilles tendon (one patient), correction of recurrent hip luxations (one patient), ligament rupture (two patients), and cervical and lumbar disk hernias (two patients). Most patients reported unsatisfactory effects of local anesthesia and oral analgesics (particularly, for the treatment of headache). In three

patients (no.s 3, 13, and 18), local anesthesia required additional administrations or the use of alternative methods (e.g., general or epidural anesthesia). Post-surgical complications included multiple keloids (no.s 8 and 18) and herniation of the underlying tissues (no. 21).

**TABLE IV. Clinical Presentations of Ehlers–Danlos Syndrome Hypermobility Type**

- [1] Recurrent articular dislocations [also after surgical repair]
- [2] Chronic/recurrent articular pain in adults or young adults with joint hypermobility [Beighton score >4] and/or a history of infancy/childhood joint hypermobility
- [3] Soft/velvety skin and/or easy bruising with joint hypermobility [Beighton score >4] or a history of infancy/childhood joint hypermobility
- [4] Chronic asthenia with recurrent articular pain and negative screening for inflammatory arthritis
- [5] Acute thoracic pain due to spontaneous rib luxation/subluxation [rare]
- [6] Early-onset uterine/vescical/rectal prolapse in nullipara [rare]

## DISCUSSION

### Diagnostic Criteria

Hypermobility type Ehlers–Danlos syndrome is a diagnosis of exclusion ruling out an underlying bone dysplasia or neuromuscular disorder (such as Bethlem myopathy) and various similar connective tissue disorders, including other types of EDS and the fibrillinopathies. Diagnosing is difficult due to the lack of a major clinical trait (except for joint hypermobility) and specific diagnostic laboratory tests. Although tenascin-X monoallelic or biallelic inactivation is claimed as responsible for HT-EDS, mutations in this gene can be documented in no more than 10% of the patients [Schalkwijk et al., 2001; Zweers et al., 2003]. Therefore, the need for diagnostic criteria becomes evident. In the revised Villefranche classification of EDS, major (i.e., skin involvement and generalized joint hypermobility) and minor (i.e., recurring joint dislocations, chronic joint/limb pain, and positive family history) criteria are identified [Beighton et al., 1998]. Alternative criteria are also proposed [Levy, 2007]. However, application of these criteria may be difficult in specific cases, also because they do not consider frequent additional complications such as pelvic dysfunction, gastrointestinal involvement, and chronic asthenia, as well as the evolution of the phenotype (see below). On the other hand, an accurate and revised set of diagnostic criteria is published for JHS, which is an apparently mild phenotype with multiple overlaps of many heritable connective tissue disorders [Grahame, 2000]. It has become evident that HT-EDS and JHS most probably represent the same condition and that HT-EDS is the default diagnosis in children, while JHS is the term typically used to label adult patients [Tinkle et al., 2009]. The need for a more unified set of diagnostic criteria is urgent, also because an HT-EDS child usually will lose the overt joint hypermobility and become a JHS adult with a series of late-onset complications which need accurate screening, early diagnosis and, possibly, appropriate treatment.

### Clinical Presentation

Joint hypermobility may present with a wide variety of musculoskeletal symptoms [Hakim and Grahame, 2003]. In our experience, evaluation was requested by patients with a very limited number of presenting manifestations (Table IV). Each of them probably reflected the “personal” point of view of the referring physician (e.g., soft/velvety skin and/or easy bruising with joint hypermobility or a history of infancy/childhood joint hypermobility) and, therefore, may represent a possible bias. However, in our opinion, it is very likely that these six possible clinical presentations represent most HT-EDS patients. Accordingly, we emphasize that HT-EDS should be first considered in subjects referred for any of the tabulated clinical problems. This should lead to a rapid identification of these patients with significant advantages for their quality of life.

### Evolution and Main Manifestations

In our cases, mucocutaneous involvement is always of mild degree and with minimal clinical consequence. However, if accurately investigated, it may be essential for diagnosis. At variance with

other EDS types, in HT-EDS, motor development and pregnancy usually evolved uneventful, and cardiovascular involvement, although common, has no significant effect on the general health of these patients. Conversely, the most serious clinical implications of HT-EDS, in terms of marked deterioration of the quality of life, are related to musculoskeletal, neurological, and gastrointestinal involvement. Many of the associated symptoms cannot be investigated and confirmed by laboratory or instrumental tests. This lack of evidence and absence of additional clear-cut traits (as usually occurs in other EDS variants such as atrophic scars in the classical type, or vascular accident and internal organ rupture in the vascular one) inevitably causes a delay in diagnosis.

With accurate clinical history records and by comparing findings among subjects at different ages, we were able to delineate the natural history of HT-EDS. Our insights are well in accordance with previous observations [Gurley-Green, 2001; Steinmann et al., 2002]. The natural history of this condition may be considered in three phases. Since the very first months of life, all patients displayed marked ligamentous laxity which permitted them to contort their body, perform splits, and assume strange positions by facultative subluxations (“hypermobility” phase). Many patients undertook sports which are facilitated by joint hypermobility such as ballet and gymnastics. During infancy and childhood many patients never complained of articular/muscular pain, although recurrent/chronic arthralgias, and myalgias may appear early in life. In this phase, the most consistent clinical sign is joint instability and recurrent dislocations (especially at knees). Occasionally, the combination of articular pain and instability may cause children to miss school. The second phase (“pain” phase) usually starts during the second decade of life. In this period, joint hypermobility decreases (although in many patients the Beighton score is still  $>4$ ) and joint, muscle, and back pain appears. Chronic pain and joint instability progressively limit daily activity with major difficulties or impossibility in handling objects, walking for more than 30–60 min, running, and carrying heavy objects (such as shopping bags). Consequent chronic asthenia and sleep disturbances have a major impact on working capacities and quality of life. Pain avoidance can lead to reduce physical activity with consequent muscular deconditioning and atrophy. In this phase, additional neurological changes usually appear. Subluxations and luxations may become habitual or chronic, especially at the temporomandibular joints. The third phase (“stiffness” phase) develops later. It is characterized by progressive limitation of joint motion (with negative Beighton score) and accentuation or reduction of vertebral curvatures. In this phase, the quality of life is particularly affected and anxiety and depression are common.

Although in most patients we were able to identify the various phases of this progression, accumulated data are too scanty to define specific age groups. Such a paradoxical evolution (from joint hypermobility to stiffness) points out the difficulties in making a diagnosis. Physical examination may fail to demonstrate overt joint hypermobility in symptomatic patients and this may falsely lead the exclusion of the diagnosis [Grahame and Bird, 2001]. Consequently, accurate clinical history records are essential for reaching the diagnosis.

## Additional Complaints

Gastrointestinal involvement, mainly in form of gastroesophageal reflux and irritable bowel syndrome, is a well-known complication of HT-EDS [Levy et al., 1999]. More recently, it was suggested that joint hypermobility (Beighton score >3) could be more common among boys with slow transit constipation and that JHS may have a higher incidence among subjects with unexplained gastrointestinal symptoms [Reilly et al., 2008; Zarate et al., 2009]. However, the pathogenetic relationship between HT-EDS and gastrointestinal involvement is still unknown. Interestingly, we found dolichocolon in three patients always due to severe constipation and recurrent abdominal pain. Although correlation between dolichocolon and intestinal dysfunction is still debated [Müller-Lissner et al., 2005], it is possible that, in HT-EDS, congenital elongation of the colon may contribute to the abdominal symptoms.

Similarly, chronic/recurrent headache is a major complaint of HT-EDS patients, but the pathogenetic nature of this finding is largely obscure. In one patient with intractable headache we identified an Arnold–Chiari malformation type I. The hypothesis that Arnold–Chiari malformation, as a consequence of occipitotlantoaxial instability, may be more common in symptomatic HT-EDS patients is supported by the reports of EDS cases with headache and this malformation [Jacome, 1999; Jacome, 2001]. Further support is added by the recent evidence of increased incidence of hereditary disorders of the connective tissue among patients with Arnold–Chiari malformation [Milhorat et al., 2007].

In eight patients, we noted chronic or recurrent dysphonia, probably due to incoordination and/or hypotonia of the vocal cords. We think that this association is not coincidental, because dysphonia accords well with the hypothesis of generalized laxity of connective tissue and hypotonia observed in HT-EDS. In line with this concept, there are four previously published patients with an unclassified EDS type and dysphonia [Rimmer et al., 2008; Richmon et al., 2009]. Additional observations are needed to investigate whether dysphonia is an HT-EDS specific symptom or not.

Although based on detailed clinical evaluation, the present study suffers of major limitations. The first unresolved problem is the very limited number of patients. This probably reflects the general unawareness on HT-EDS. The paucity of studied subjects and the extreme variability of age at examination hamper a precise estimation of the true cross-sectional prevalence of the listed features, most of which are age-related. Secondly, many of the investigated manifestations are not uncommon in the general population. Therefore, the real increase of the risk in developing these complications for patients with HT-EDS remains largely unknown. Further studies using appropriate control population and focused on specialty aspects of HT-EDS (e.g., oral or gastrointestinal features) are expected in order to shed more light on this protean condition.

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