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Recognizing and treating Ehlers-Danlos syndrome(s): the need for a multidisciplinary approach.

Reconocimiento y tratamiento de los síndromes de Ehlers-Danlos: Necesidad de un enfoque pluridisciplinario.

Reconhecimento e tratamento das síndromes de Ehlers-Danlos: necessidade de um enfoque pluridisciplinário.

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ABSTRACT

Ehlers-Danlos syndrome groups together different inherited disorders of the soft connective tissues with systemic manifestations. The most common features include chronic/recurrent musculoskeletal pain, headache, chronic fatigue and cardiovascular dysautonomia, arterial and visceral fragility with propensity to spontaneous ruptures, functional gastrointestinal disorders, pelvic and voiding dysfunction, minor neurodevelopmental disorders and some psychiatric comorbidity. Severity and extent of such complications are strongly influenced by the clinical-molecular subtype. Hence, accurate diagnosis is pivotal for appropriate management. The proteiform manifestations of Ehlers-Danlos syndromes often request a multidisciplinary approach in the pediatric as well as adult patients. The multisystem nature of many symptoms and their still incompletely understood pathogenesis make hard to treat the complex patient, who often needs the coordinated interventions of various professionals. Due to the lack of a consensus on the treatment of Ehlers-Danlos syndromes, here the authors report their experience and a proposal.

Keywords: diagnosis, Ehlers-Danlos syndrome, fatigue, joint hypermobility, management, pain.

RESUMEN

El grupo de síndromes de Ehlers-Danlos reúne diferentes trastornos hereditarios del tejido conectivo con manifestaciones sistémicas. Las características más comunes incluyen dolor musculoesquelético crónico/recurrente, cefalea, fatiga crónica, disautonomía cardiovascular, fragilidad arterial y visceral con propensión a rupturas espontaneas, trastornos gastrointestinales funcionales, trastornos pélvicos y de micción, trastornos menores del neurodesarrollo y algunas comorbilidades psiquiátricas. La gravedad y el alcance de estas complicaciones están fuertemente influenciados por el subtipo clínico-molecular, por lo tanto la precisión diagnóstica es fundamental para un tratamiento apropiado. Las manifestaciones proteiformes de los síndromes de Ehlers-Danlos, requieren a menudo de un enfoque multidisciplinario en pacientes niños y adultos. La naturaleza multisistémica de muchos de los síntomas, y su aun no bien comprendida patogénesis, hacen difícil la tarea de tratar la complejidad de estos pacientes que necesitan la intervención coordinada de varios profesionales. Debido a la falta de consenso sobre el tratamiento de los síndromes de Ehlers-Danlos, los autores presentan en este trabajo su experiencia y propuestas.

Palabras clave: diagnostico, síndrome de Ehlers-Danlos, fatiga, hipermovilidad articular, tratamiento, dolor.

RESUMO

O grupo de síndromes de Ehlers-Danlos reúne diferentes transtornos hereditários do tecido conectivo com manifestações sistêmicas. As características mais comuns incluem dor musculoesquelética crônico/recorrente, cefaleia, fadiga crônica, disautonomia cardiovascular, fragilidade arterial e visceral com propensão a rupturas espontâneas, transtornos gastrointestinais funcionais, transtornos pélvicos e de micção, transtornos menores do neurodesenvolvimento e algumas comorbidades psiquiátricas. A gravidade e o alcance destas complicações estão fortemente influenciadas pelo subtipo clínico-molecular, no entanto a precisão diagnóstica é fundamental para um tratamento apropriado. As manifestações proteiformes das síndromes de Ehlers-Danlos, requerem frequentemente de um enfoque multidisciplinário em pacientes crianças e adultos. A natureza multissistêmica de muitos dos sintomas, e sua ainda não bem compreendida patogênese, fazem difícil a tarefa de tratar a complexidade destes pacientes que necessitam a intervenção coordenada de vários profissionais. Devido à falta de consenso sobre o tratamento das síndromes de Ehlers-Danlos, os autores apresentam neste trabalho sua experiência e propostas.

Palavras-chave: diagnóstico, sindrome de Ehlers-Danlos, fadiga, hipermobilidade articular, tratamento, dor.

Figura 1. Medias, desviaciones estándar y aciertos máximos que pueden ser obtenidos en cada prueba del PROLEC-R.

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Ehlers-Danlos syndrome (EDS) is an umbrella term for a clinically and genetically heterogeneous group of hereditary soft connective tissue disorders which mainly involve dermis, joints and cardiovascular system in form of abnormal skin texture, generalized joint hypermobility (gJHM) and vascular fragility (Callewaert et al., 2008). The current classification (Villefranche nosology) identifies six major EDS variants, including classic, vascular, hypermobility type (EDS-HT), kyphoscoliotic, arthrochalasis and dermatosparaxis types (Beighton et al., 1998). In the ensuing years, the number of additional, apparently rarer forms increased and no less that eleven further EDS types were identified (Castori, 2012). To date, cEDS and EDS-HT are the most commonly encountered forms. This is partly related by the clinical overlap between EDS-HT and joint hypermobility syndrome (JHS), a rheumatologic disorder dominated by chronic pain, gJHM and minor skin features and recognized by the Brighton criteria (Grahame et al., 2000; Tinkle et al., 2009).

As a whole, EDS is considered a rare condition based on early prevalence data fixing a frequency of ~1:5,000 in the general population (Steinmann et al., 2002). However, EDS is likely an underdiagnosed disorder as some authors suggest a frequency of 0.75-2% for symptomatic gJHM (Hakim & Sahota, 2006). For years, such a discrepancy was determined by the lack of clearness concerning the existence of EDS-HT and JHS as distinct entities, and the absence of well defined diagnostic criteria. Recently, segregation study demonstrated clinical identity between JHS and EDS-HT (i.e. JHS/EDS-HT) in familial cases (Castori et al., 2014), and a project for identifying an entirely novel set of diagnostic criteria is going to be finalized by the joined efforts of the Ehlers-Danlos National Foundation and Ehlers-Danlos Support UK. Unfortunately, JHS/EDS-HT is still without a known molecular basis and its definition remains a matter of debate (De Paepe & Malfait, 2012).

EDS is a complex disorder with protean manifestations and often characterized by a late diagnosis (*The voice of 12,000 patients*, at http://www.eurordis.org/it/publication/voice-12000-patients). Unpublished experience in most Italian specialized centers tells us that many EDS patients have an acceptable quality of life and do not present severe complications (Castori, personal communication). Anyway, multisystemic involvements are a characterizing feature of EDS and they may present with a variable mixture of chronic pain and fatigue, multiorgan disabilities, increased incidence of surgical complications and potentially life-threatening cardiovascular events. The chance and overall severity of these manifestations varies among patients and EDS subtypes. For this reason, early and accurate patients' classification is crucial for minimizing symptom severity and prevents complications (Castori & Colombi, 2016). Still in line with the need of a coordinated and standardized approach to diagnose and manage the various types of EDS, the Ehlers-Danlos National Foundation and Ehlers-Danlos Support UK are nurturing an international consensus of experts who will conclude their work on 2017.

In the meanwhile, the number of suspected patients is increasing in many countries and their complaints need a multidisciplinary approach. The aim of this paper is to present an approach to diagnose and manage EDS patients in order rise the attention of other specialists on the ramifications that this disorder has in the various medical disciplines.

Diagnosis in brief

Most EDS clinical subtypes are first suspected by general practitioners and specialists in selected clinical scenarios, comprising (i) generalized joint hypermobility with or without recurrent complications related to joint instability (e.g. dislocations and soft-tissue injuries in multiple body sites); (ii) early onset cutaneous and/or capillary fragility once excluded hematologic and other more common disorders; (iii) chronic/recurrent and diffuse non-inflammatory musculoskeletal pain; (iv) unusual body *habitus* especially in presence of additional features of soft connective tissue dysfunctions;

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and (v) vascular accidents especially without other risk factors and/or in multiple sites and/or with positive family history of sudden death. If ascertained by one or more of the above listed presentations, the patient should be referred to specialized clinics in order to substantiate the suspect and, if necessary, carry other more specific investigations for differential diagnosis and/or diagnosis confirmation. Although most EDS variants have known molecular bases and available confirmatory tests, many patients are affected by JHS/EDS-HT, which still remain without a laboratory proof. Hence, the diagnosis of EDS is essentially clinical. Molecular (or other intermediate) tests are feasible only for patients (suspected) affected by other EDS variants; in these cases, confirmatory investigations are mandatory. Differential diagnosis should be focused in excluding any other acquired conditions mimicking the above listed presentations and differentiating EDS from other partially overlapping hereditary soft connective tissue disorders, such as Loeys-Dietz and Marfan syndromes, which have distinct natural histories as well as monitoring and familial implications.

Multidisciplinary approach

Due to the extreme clinical variability and existence of genotype-phenotype correlations, it is strictly recommended to coordinate prevention and management in highly specialized services with a strong clinical genetic background. Diagnosis is usually established at consultation (pediatrics and clinical genetics), based on family and personal history, physical examination and results of selected investigations (particularly, heart ultrasound at rest and full ophthalmologic exam with slit-lamp examination). The support of a genetic laboratory with a highly technological expertise is needed in order to confirm the diagnosis in EDS subtypes with a known molecular basis. Once the diagnosis is established by the case manager, further baseline investigations are indicated based on available general recommendations by major subtypes (Levi, 2012; Malfait et al., 2011; Pepin & Byers, 2011; Yeowell and Steinmann, 2008) and literature (Gulbahar et al., 2006, McDonnell et al., 2006; Malfait and De Paepe, 2009; Danese et al., 2011; Gharbyia et al., 2012; Jackson et al., 2012). The results of these investigations are aimed at identifying and quantifying the involvement of tissues and organs commonly involved in the major EDS variants. Useful baseline investigations include bone mass densitometry, non-invasive exclusion of common gastrointestinal co-morbidities (i.e. celiac disease, vitamin D malabsorption/insufficiency, lactose intolerance and sideropenic anemia) and first-level testing for bleeding disorders (i.e. full blood count, VWF:Ag, VWF: RCo, FVIII:C, platelet aggregation test and bleeding time testing). Literature data are too scanty for the rarer subtypes. A conservative approach suggests to prescribe baseline investigations also to these patients.

In order to disclosing and evaluating common co-morbidities, including recurrent/chronic musculoskeletal pain, cardiovascular involvement, dysautonomia, functional gastrointestinal disorders, pelvic dysfunction, psychiatric manifestations and neurodevelopmental attributes, second-line consultations should be considered. Accordingly, the multispecialty evaluation team of a patient with a recent diagnosis of EDS and one or more satellite manifestations may include one or more of the following: rheumatologist, orthopedic surgeon, pain specialist, cardiologist, vascular and chest surgeons, pelvic specialist, (neuro) gastroenterologist, child neurologist, clinical psychologist and psychiatrist. The case manager should encourage all specialists to periodically share their reports, treatment prescriptions and suggestions on every patient in order to prioritize management and avoid potentially conflicting therapeutic suggestions. Such an exchange, coordinated by the case manager, is pivotal for referring the patient to selected treatment teams for (i) musculoskeletal pain and motor disability, (ii) headache and other head pain, (iii) monitoring cardiovascular risk and treating dysautonomia, (iv) gastrointestinal and pelvic dysfunctions, (v) neurodevelopmental and psychiatric disorders (Table 1).

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Table 1. A proposal of management teams for selected manifestations of Ehlers-Danlos syndromes.

Musculoskeletal pain and motor disabilities	Headache	Cardiovascular risk and dysautonomia	Gastrointestinal and pelvic dysfunction	Neurodevelopmental and psychiatric issues
Physiatrist	Neurologist	Cardiologist	(Neuro)-gastroenterologist	Child neurologist
Orthopedist	Orthodontist	Neurologist (ANS specialist)	Gynecologist	Developmental pediatrician
Pain specialist	Gnathologist/TMJ specialist	Chest surgeon	Urologist	Psychiatrist
Neurologist	Physical therapist (TMJ)	Vascular surgeon	Pelvic surgeon	Clinical psychologist
Physical therapist	Neurosurgeon	Cardiovascular rehabilitation specialist	Physical therapist (pelvis)	Physical therapist (childhood)
Occupational therapist			Neurosurgeon	Speech therapist
Osteopath				
Non-traditional medicine specialist				

ANS, autonomic nervous system; TMJ, temporomandibular joint.

Chronic pain and headache

In EDS, particularly JHS/EDS-HT, musculoskeletal pain and fatigue represent major disability determinants (Voermans et al., 2010a; Voermans and Knoop, 2011). In the recent past, great importance was given to the evolution of pain in JHS/EDS-HT. It usually starts at joints, in form of occasional or recurrent arthralgias especially at lower limbs and are often interpreted as "growing pain". By the years, arthralgias increase in frequency, intensity and number of affected sites. In a more advanced phase, musculoskeletal pain is widespread and chronic with many neuropathic features (Castori et al., 2013). While propensity to micro- and macrotraumatism may be easily considered a trigger for recurrent arthralgias, this is not the case in patients with chronic pain. In these individuals, hyperalgesia and central sensitization play a major role (Rombaut et al., 2015; Di Stefano et al., 2016). Transition from recurrent arthralgias to chronic widespread pain, which occurs in a patients' subgroup, strongly affects quality of life. As in EDS, similarly to other rheumatologic disorders, chronic pain is hardly managed, contemporary treatment is mostly focused on preventing such a transition. In patients with minimal or moderate pain and preserved quality of life, treatment and prevention are focused on physical exercise and limited use of painkillers (especially,

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ibuprofen, paracetamol and naproxen at full dosage). In more advanced stages, multidisciplinary approach to pain is essential and should consist in a tailored mixture of physical therapy, adapted physical exercise, painkiller use, psychotherapy and education of the patient and family. Major opioids are typically contraindicated in EDS, while minor opioids, myorelaxants and drugs for neuropathic pain should be prescribed with caution.

Headache is a specific type of pain which is quite common in EDS (Sacheti et al., 1997). Various forms of headache are theoretically more common in EDS due to congenital laxity of non-ossified connective tissues and comprise migraine, headache attributed to temporomandibular joint disorder, cervicogenic headache, new daily headache, neck-tongue syndrome, and headache attributed to Chiari malformation and to spontaneous low cerebrospinal fluid pressure (Castori et al., 2015). In JHS/EDS-HT, migraine is the most common clinical form of headache (Bendik et al., 2011; Granata et al., 2014). Sometimes, patients describe the co-existence of two or more types of headache, simultaneously or separately. Too scanty data are available on the underlying pathogenesis and, consequently, on evidence-based treatments. Standard anti-migraine drugs are considered efficacious especially if supported by psychological support comprising relaxation techniques, biofeedback and cognitive-behavioral therapy. Very preliminary evidence suggests further potentially valid resources for head/neck pain, such as physical therapy focused on treating the temporomandibular joint (Pangarkar & Lee, 2011; Vernon & Humphreys, 2008), orofacial myofunctional therapy (de Felicio et al., 2010), and other non-traditional therapies such as (gentle) chiropratics (Colloca & Polkinghorn, 2003) and acupuncture (Martin & Neilson, 2014). Management of sleep disturbance, avoiding opioid and other painkiller overuse, and preventing transition to chronic pain (i.e. pain sensitization) are other useful management issues to be addressed for an optimal treatment strategy.

Dysautonomia and the cardiovascular risk

Cardiovascular dysautonomia was first identified in EDS by Rowe et al. (1999) and their observation was subsequently confirmed. While an autonomic burden is common in EDS, JHS/EDS-HT patients suffer more than those with EDS classical and vascular types (De Wandele et al., 2014a). Actually, JHS/EDS-HT is the best studied EDS subtype and in this condition there are a higher low frequency/high frequency ratio (i.e. an increase of the physiological heart rate variability), a greater blood pressure fall during Valsalva manoeuvre and a smaller initial systolic blood pressure increase during tilting (De Wandele et al., 2014b). Postural orthostatic tachycardia (syndrome) is the most common neurophysiological profile in JHS/EDS-HT, but some patients can present with neuromediated hypotension or, paradoxically, orthostatic hypertension. Chronic fatigue is one of the most common manifestation of postural arthostatic tachycardia (Mathias et al., 2011; Bravo, 2015) and is highly represented in EDS (Voermans et al., 2010b). Management of cardiovascular dysautonomia is essentially based on non-pharmacological and prevention strategies, while the use of anti-hypotensive drugs is usually limited to the most severely affected individuals in whom other approaches resulted unsuccessful (Mathias et al., 2011).

Mitral or other cardiac valve prolapse/insufficiency is considered a common finding in most EDS subtypes. However, rarely it represents a real clinical problem and does not need specific management in most cases. Classic EDS and JHS/EDS-HT may also present aortic root dilatation (10-13%). At difference with other hereditary soft connective tissue disorders, aortic root dilatation is a benign trait in classic EDS and JHS/EDS-HT and is often non-progressive after puberty/adolescence (Tiller et al., 1998; Wenstrup et al., 2002; McDonnell et al., 2006). Therefore, pharmacologic prevention of aneurysm rupture is still questioned in classic EDS and JHS/EDS-HT. Additionally, clinically insignificant cardiac findings

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in classic EDS and JHS/EDS-HT include impaired left ventricular relaxation, elongated cardiac silhouette and prominent right coronary artery (McDonnell et al., 2006). In contrast to classic EDS and JHS/EDS-HT, vascular EDS features has strong increase of the cardiovascular risk, fragility of the aorta, and medium and small sized arteries. Arterial ruptures with or without a pre-existing aneurysm and dissections may occur everywhere. This determines a high risk for life-threatening complications and a reduced life span in vascular EDS (Beighton et al., 1998). Treatment of acute manifestations of vascular EDS should be managed by expert professionals and the follow-up should be always preceded by counseling of the patient and family, and carried out preferring non-invasive approaches. A single study demonstrates three-fold reduction of risk in arterial rupture in vascular EDS by the use of the beta-blocker celiprolol (Ong et al., 2010). These considerations may be equally applied to other EDS variants with vascular fragility, such as kyphoscoliotic EDS and classic EDS with arterial fragility due to *COL1A1* mutations.

Gastrointestinal and pelvic dysfunction

Practice indicates a common gastrointestinal and pelvic involvement in EDS. Many published studies are focused on JHS/EDS-HT, although gastrointestinal and pelvic manifestations are repeatedly described also in classic and vascular EDS (Castori et al.,2015). Structural abnormalities related to laxity of viscera, ligaments, abdominal wall and pelvis include abdominal hernias, rectal/pelvic prolapse, visceral ptosis, hiatus hernias, dolichocolon, intussusceptions, malrotation and diverticula. Their management usually follows standard procedures especially in EDS subtypes with mild or moderate tissue fragility. In EDS variants with marked tissue and vascular fragility, the choice between surgery and conservative treatment should be carefully tailored. Functional disorders comprising dysphagia, gastroesophageal reflux, dyspepsia, irritable bowel disease, underactive or overactive bladder and constipation are leading visceral manifestations in JHS/EDS-HT. For these manifestations, exclusion of common co-morbidities (e.g. celiac disease, lactose intolerance, small bowel bacterial overgrowth and infections) is recommended in most cases. Standard endoscopic examinations do not have a formally increased risk in EDS variants without increased visceral fragility, but often lead to negative or inconsistent results. The utility of specific functional tests is still questioned in EDS (Zarate et al., 2010). Treatment of functional gastrointestinal manifestations as well as pelvic dysfunctions are often unsuccessful and the improvement of symptoms is reached mostly by tailored nutritional therapy, non traditional approaches and pelvic floor training rather than standard pharmacologic strategies. Vascular EDS and other variants with increased vascular fragility may present with acute abdominal symptoms due to spontaneous arterial and/or abdominal viscera ruptures. Also in this case, the choice between surgery and conservative management is a challenge and, ideally, should be performed in highly specialized centers. As most of these complications occurs abruptly, all affected individuals with EDS variants with vascular fragility should be supplied by rapid consultation sheets and/or direct contact resources for the unexperienced professionals that patients may encounter far away from their reference center.

Psychiatric and neurodevelopment disorders

Available literature suggests a non-casual association between gJHM, JHS/EDS-HT and impaired motor coordination, including motor delay, poor sensorimotor coordination, clumsiness, poor balance, difficult in handwriting and postural control. Most of these features are observed in children with developmental coordination disorder (DCD). Accordingly, Adib et al. (2005) reported clumsiness and poor coordination symptoms in 125 children with JHS/EDS-HT. In twin studies, Kirby and colleagues suggested functional similarities between

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children with DCD and those with gJHM or JHS/EDS-HT (Kirby et al., 2005; Kirby & Davies, 2007). A link between connective tissue and DCD is also supported by the observation of a high prevalence of gJHM in children with DCD (Jelsma et al., 2013). Other works illustrated reduced proprioception in children and adults with gJHM especially at lower limbs (Smith et al., 2013) and at the proximal interphalangeal joints of fingers (Mallik et al., 1994). Hence, It was supposed that impaired proprioception may be the background dysfunction contributing to defective gross motor and fine motor coordination skills in gJHM and JHS/EDS-HT (Ghibellini et al., 2015). Attention deficit/hyperactivity disorder (ADHD) frequently accompanies DCD and may also affect with a higher frequency individuals with gJHM (Harris, 1998; Koldas Dogan et al., 2011; Hollertz, 2012; Shiari et al., 2013; Castori et al., 2014).Speech and language disorders and poor writing skills might be more frequent in subjects with gJHM and JHS/EDS-HT with an impact on academic performances (Averdson & Heintskill, 2009).

Psychological distress is a known feature of gJHM and EDS. This association has been studied since 1988, when Bulbena and co-workers identified a significantly higher rate of panic disorder, agoraphobia, and simple phobia in a sample of hypermobile subjects compared with non-hypermobile subjects (Bulbena et al., 1988). The most frequently described association is with anxiety and related disorders (Bulbena et al., 1988, 1993, 2006, 2011; Martín-Santos et al., 1998; Gulsun et al., 2007; Ercolani et al., 2008; García Campayo et al., 2010; Gürer et al., 2010; Baeza-Velasco et al., 2011, 2014, 2015; Pailhez et al., 2011, 2014; Murray et al., 2013). Some studies found a positive association between gJHM or JHS/EDS-HT and depression (Bulbena et al., 1993, 2011; Ercolani et al., 2008; Gürer et al., 2010; Lumley et al., 1994; Murray et al., 2013). Connections with autism spectrum disorders (Tantam et al., 1990; Fehlow and Tennstedt, 1985; Sieg, 1992; Takei et al., 2011) and obsessive–compulsive personality disorder (Pasquini et al., 2014) were also preliminary found.

These findings and clinical practice highlight the importance of paying attention on motor impairment, inattention and hyperactivity, speech difficulties or language delay, learning disabilities and psychiatric manifestations in patients affected by EDS. In the suspect of one or more of the above mentioned co-morbidities referral to child neurologist, clinical psychologist or psychiatrist is highly recommended. Psychiatric and neurodevelopment co-morbidities significantly contribute to worsening of quality of life in affected individuals. Accordingly, psychological support is crucial and should be high considered (Ghibellini et al., 2015).

Surgical and anesthetic issues

In EDS, tissue fragility and hyperextensibility and delayed wound healing may predispose to ruptures of organs and vessels, visceral ptoses, increases mobility of the intrabdominal viscera with a theoretically augmented risk of intussusceptions and functional symptoms, as well as minor or major intraoperatory or postsurgery complications. The rate and severity of such complications is strongly influenced by the EDS subtype. Hence, the need of accurate differential diagnosis at the assessment stage. In subtypes with increased vascular fragility (i.e. vascular EDS, classic EDS with arterial rupture due to mutations in *COL1A1* and kyphoscoliotic EDS) invasive surgery is generally not recommended and should be always postponed except for emergency or in case of elective surgery with documented or strongly presumed efficacy in EDS. In all other variants, surgery may be successfully performed if carried out following general recommendations, that comprise: (i) minimal surgical dissection and use of minimal lateral force during incisions, retraction and suturing; (ii) haemostasis may be difficult and the use of vessel clamping should be avoided or, at least, held lightly due to the risk of tearing; (iii) skin closure should be performed in two layers (subcutaneous and cutaneous) with minimal tension, sufficient amount of sutures, deep stitches and the support of steristrips,

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by using proper distance to the incision without the use of skin clips; (iv) sutures should be left twice as long as normally recommended in order to avoid wound re-opening (Berney et al. 1994; Malfait and De Paepe, 2009). Further considerations on gastrointestinal surgery are available in the review paper by Burcharth and Rosenberg (2012). Also anesthesia and perioperative management need a tailored approach. Although major complications are rare in many EDS subtypes, efficacy of these procedures may be influenced by some primary EDS features, including vascular, thecal and mucosal fragility, propensity to ecchymoses and the risk of hemorrhage, as well as some common co-morbidities, mostly including autonomic dysfunction, occipitoatlantoaxial joint instability and spondylosis. A freely downloadable summary of recommendations for the anesthesiologist are available at the OrphanAnesthesia website (http://www.orphananesthesia.eu/en/rare-diseases/published-guidelines/cat_view/61-rare-diseases/60-published-guidelines/89-ehlers-danlos-syndrome.html) or in the work by Wiesmann et al. (2014).

Pediatric-adulthood healthcare transition

Transition of care from child to adult specialists in chronic disorders with onset in the pediatric age is one of the major challenges of modern medicine and its system-based approach. EDS, as a multisystem condition with many congenital or early-onset manifestations, is exemplificative of the actual difficulties and patients face this further source of burden and confusion. To date, literature is scanty of data concerning this issue and its potential impact on patients' wellbeing and prognosis. Anyway, the attention that recently was put on the evolving natural history of JHS/EDS-HT (Castori et al., 2013) and, consequently, in the other common variants highlights an unexpectedly wide spectrum of possible clinical manifestations, which are strongly influenced by age. Accordingly, while the clinical/molecular diagnosis remains the same across the various ages, this does not always hold true for patients' reason for referral and appropriate differential diagnosis. Ideally, a multidisciplinary team approaching and following this type of chronic patients should remain the same at the various ages. The increasing expertise that the, still few, specialized centers are coalescing around EDS in various countries and the emerging need of identifying a core of skilled specialists able to face selected management issues at different ages will likely contribute in guiding a more fluid pediatric-adulthood transition in EDS.

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REFERENCIAS

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

Arverdson, JC., Heintskill, B. (2009) Chapter 27. Ehlers-Danlos syndrome. In: *Clinical management of sensorimotor speech disorders, second edition*. McNeil MR, editor. New York, US: Thieme. 314-316.

Baeza-Velasco, C., Gely-Nargeot, MC., Vilarrasa, AB., Fenetrier, C., Bravo, JF. (2011) Association between psychopathological factors and joint hypermobility syndrome in a group of undergraduates from a French university. *International Journal of Psychiatry in Medicine 41*: 187-201.

Baeza-Velasco, C., Stoebner-Delbarre, A., Cousson-Gélie, F., Pailhez, G., Bulbena, A., Baguet, F., Gély-Nargeot, MC. (2015) Increased tobacco and alcohol use among women with joint hypermobility: a way to cope with anxiety? *Rheumatology International 35*: 177-181.

Beighton, P., De Paepe, A., Steinmann, B., Tsipouras, P., Wenstrup, RJ. (1998) Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). *American Journal of Medical Genetics 77*: 31-37.

Bendik, EM., Tinkle, BT., Al-shuik, E., Levin, L., Martin, A., Thaler, R., Atzinger, CL., Rueger, J., Martin, VT. (2011) Joint hypermobility syndrome: A common clinical disorder associated with migraine in women. *Cephalalgia 31*: 603-613.

Berney, T., La Scala, G., Vettorel, D., Gumowski, D., Hauser, C., Frileux, P., Ambrosetti, P., Rohner, A. (1994) Surgical pitfalls in a patient with type IV Ehlers-Danlos syndrome and spontaneous colonic rupture. Report of a case. *Diseases of the Colon & Rectum 37*: 1038-1042.

Bravo, JF. (2015) La dysautonomie dans le syndrome Ehlers-Danlos type III. *Journal de Réadaptation Medicale 36*: 52-55.

Bulbena, A., Duro, JC., Mateo, A., Porta, M., Vallejo, J. (1988) Joint hypermobility syndrome and anxiety disorders. *Lancet 17*: 694.

Bulbena, A., Gago, J., Pailhez, G., Sperry, L., Fullana, MA., Vilarroya, O. (2011) Joint hypermobility syndrome is a risk factor trait for anxiety disorders: a 15-year follow-up cohort study. *General Hospital Psychiatry 33*: 363–370.

Bulbena, A., Duró, JC., Porta, M., Martín-Santos, R., Mateo, A., Molina, L., Vallescar, R., Vallejo, J. (1993) Anxiety disorders in the joint hypermobility syndrome. *Psychiatry Research 46*: 59-68.

Bulbena, A., Gago, J., Sperry, L., Bergé, D. (2006) The relationship between frequency and intensity of fears and a collagen condition. *Depression & Anxiety 23*: 412-417.

Burcharth, J., Rosenberg, J. (2012) Gastrointestinal surgery and related complications in patients with Ehlers-Danlos syndrome: a systematic review. *Digestive Surgery 29*: 349-357.

Callewaert, B., Malfait, F., Loeys, B., De Paepe, A. (2008) Ehlers-Danlos syndromes and Marfan syndrome. *Best Practice & Research: Clinical Rheumatology 22*: 165-189.

Castori, M., Colombi, M. (2015) From the beside to the bench and backwards:diagnostic approach and management of Ehlers-Danlos syndrome(s) in Italy. *Journal de Réadaptation Medicale 36*: 9-27.

Castori, M., Dordoni, C., Valiante, M., Sperduti, I., Ritelli, M., Morlino, S., Chiarelli, N., Celletti, C., Venturini, M., Camerota, F., Calzavara-Pinton, P., Grammatico, P., Colombi, M. (2014) Nosology and inheritance pattern(s) of joint hypermobility syndrome and Ehlers-Danlos syndrome, hypermobility type: a study of intrafamilial and interfamilial variability in 23 Italian pedigrees. *American Journal of Medical Genetics Part A 164A*: 3010-3020.

Castori, M., Morlino, S., Celletti, C., Ghibellini, G., Bruschini, M., Grammatico, P., Blundo, C., Camerota, F. (2013) Re-writing the natural history of pain and related symptoms in the joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type. *American Journal of Medical Genetics Part A 161A*: 2989-3004.

Castori, M., Morlino, S., Ghibellini, G., Celletti, C., Camerota, F., Grammatico, P. (2015) Connective tissue, ehlers-danlos syndrome(s), and head and cervical pain. *American Journal of Medical Genetics Part C Seminars in Medical Genetics 169C*: 84-96.

Castori, M. (2012) Ehlers-Danlos syndrome, hypermobility type: an underdiagnosed hereditary connective tissue disorder with mucocutaneous, articular, and systemic manifestations. *ISRN Dermatology 2012*: 751768.

Castori, M., Morlino, S., Pascolini, G., Blundo, C., Grammatico, P. (2015) Gastrointestinal and nutritional issues in joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type. *American Journal of Medical Genetics Part C Seminars in Medical Genetics 169C*: 54-75.

Colloca, CJ., Polkinghorn, BS. 2003. Chiropractic management of Ehlers-Danlos syndrome: a report of two cases. *Journal of Manipulative & Physiological Therapeutics 26*: 448-459.

Danese, C., Castori, M., Celletti, C., Amato, S., Lo Russo, C., Grammatico, P., Camerota, F. (2011) Screening for celiac disease in the joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type. *American Journal of Medical Genetics Part A 155A*: 2314-2316.

de Felício, CM., de Oliveira, MM., da Silva, MA. (2010) Effects of orofacial myofunctional therapy on temporomandibular disorders. *Cranio 28*: 249-259.

De Paepe, A., Malfait, F. (2012) The Ehlers-Danlos syndrome, a disorder with many faces. *Clinical Genetics 82*: 1-11.

De Wandele, I., Calders, P., Peersman, W., Rimbaut, S., De Backer, T., Malfait, F., De Paepe, A., Rombaut, L. (2014a) Autonomic symptom burden in the hypermobility type of Ehlers-Danlos syndrome: a comparativestudy with two other EDS types, fibromyalgia, and healthy controls. *Seminars in Arthritis & Rheumatism 44*: 353-361.

De Wandele, I., Rombaut, L., Leybaert, L., Van de Borne, P., De Backer, T., Malfait, F., De Paepe, A., Calders, P. (2014b) Dysautonomia and its underlying mechanisms in the hypermobility type of Ehlers-Danlos syndrome. *Seminars in Arthritis & Rheumatism 44*: 93-100.

Di Stefano, G., Celletti, C., Baron, R., Castori, M., Di Franco, M., La Cesa, S., Leone, C., Pepe, A., Cruccu, G., Truini, A., Camerota, F. (2016) Central sensitization as the mechanism underlying pain in joint hypermobility syndrome/ Ehlers-Danlos syndrome, hypermobility type. *European Journal of Pain*. doi: 10.1002/ejp.856.

Ercolani, M., Galvani, M., Franchini, C., Baracchini, F., Chattat, R. (2008) Benign joint hypermobility syndrome: psychological features and psychopathological symptoms in a sample pain-free at evaluation. *Perceptual and Motor Skills 107*: 246-256.

VOLUMEN 10. SPECIAL ISSUE 2016. DOI: 10.7714/CNPS/10.4.207

Fehlow, P., Tennstedt, A. 1985. Neuropsychiatrische Begleitsymptome bei einem Fall von Ehlers-Danlos-Syndrom. *Psychiatrie, Neurologie, und medizinische Psychologie 37*: 215-220.

Garcìa Campavo, J., Asso, E., Alda, M., Andres, EM., Sobradiel, N. (2010) Association Between Joint Hypermobility Syndrome And Panic Disorder: A Case–Control Study. *Psychosomatics 51*: 55–61.

Gharbiya, M., Moramarco, A., Castori, M., Parisi, F., Celletti, C., Marenco, M., Mariani, I., Grammatico, P., Camerota, F. (2012) Ocular features in joint hypermobility syndrome/ehlers-danlos syndrome hypermobility type:a clinical and in vivo confocal microscopy study. *American Journal of Ophthalmology 154*: 593-600.

Ghibellini, G., Brancati, F., Castori, M. (2015) neurodevelopmental attributes of joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type: update and perspectives. *American Journal of Medical Genetics Part C Seminars in Medical Genetics 169C*: 107-116.

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

Granata, G., Padua, L., Celletti, C., Castori, M., Saraceni, VM., Camerota, F. (2013) Entrapment neuropathies and polyneuropathies in joint hypermobility syndrome/Ehlers-Danlos syndrome. *Clinical Neurophysiology 124*: 1689-1694.

Gulbahar, S., Sahin, E., Baydar, M., Bircan, C., Kizil, R., Manisali, M., Akalin, E., Peker, O. (2006) Hypermobility syndrome increases the risk for low bone mass. *Clinical Rheumatology 25*: 511-514.

Gulsun, M., Yilmaz, MB., Pinar, M., Tonbul, M., Celik, C., Ozdemir, B., Dumlu, K., Erbas, M. (2007) Thorax deformity, joint hypermobility, and anxiety disorders. *Saudi Medical Journal 28*: 1840-1844.

Gürer, G., Şendur, F., Gültekin, BK., Özcan, ME. (2010) The anxiety between individuals with and without joint hypermobility. *European Journal of Psychiatry 24*: 205-209.

Hakim, AJ., Sahota, A. (2006) Joint hypermobility and skin elasticity: the hereditary disorders of connective tissue. *Clinical Dermatology 24*: 521-533.

Harris, MJ. (1998) ADD/ADHD and hypermobile joints. *Journal of Paediatrics and Child Health 34*: 400-401.

Hollertz, O. (2012) Searching for a biological marker common for both ADHD and EDS. *Lakartidningen 109*: 41-42.

Jackson, SC., Odiaman, L., Card, RT., van der Bom, JG., Poon, MC. (2013) Suspected collagen disorders in the bleeding disorder clinic: A case-control study. *Haemophilia 19*: 246-250.

Jelsma, ,LD., Geuze, RH., Klerks, MH., Niemeijer, AS., Smits-Engelsman, BC. (2013) The relationship between joint mobility and motor performance in children with and without the diagnosis of developmental coordination disorder. *BMC Pediatrics 13*: 35.

Kirby, A., Davies, R., Bryant, A. (2005) Hypermobility syndrome and developmental coordination disorder: similarities and features. *International Journal of Therapy and Rehabilitation 12*: 431-436.

Kirby, A., Davies, R. (2007) Developmental coordination disorder and joint hypermobility syndrome - overlapping disorders? Implications for research and clinical practice. *Child: Care, Health and Development 33*: 513-519.

Koldas Dogan, S., Taner, Y., Evcik, D. (2011) Benign joint hypermobility syndrome in patients with attention deficit/hyperactivity disorders. *Turkish Journal of Rheumatology 26*:187-192.

Levy, HP. (2012) Ehlers-Danlos Syndrome, Hypermobility Type. In: Pagon RA, Bird TD, Dolan CR, Stephens K, Adam MP (editors). *GeneReviews*™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016.

Lumley, MA., Jordan, M., Rubenstein, R., Tsipouras, P., Evans, MI. (1994) Psychosocial functioning in the Ehlers-Danlos syndrome. *American Journal of Medical Genetics 53*: 149-152.

Malfait, F., De Paepe, A. (2009) Bleeding in the heritable connective tissue disorders: mechanisms, diagnosis and treatment. *Blood Reviews 23*: 191-197.

Malfait, F., Wenstrup, R., De Paepe, A. (2011) Ehlers-Danlos Syndrome, Classic Type. In: Pagon RA, Bird TD, Dolan CR, Stephens K, Adam MP (editors). *GeneReviews*™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016.

Mallik, AK., Ferrell, WR., McDonald, AG., Sturrock, RD. (1994) Impaired proprioceptive acuity at the proximal interphalangeal joint in patients with the hypermobility syndrome. *British Journal of Rheumatology 33*: 631-637.

Martin, VT., Neilson, D. (2014) Joint hypermobility and headache: the glue that binds the two together - part 2. *Headache 54*: 1403-1411.

Martín-Santos, R., Bulbena, A., Porta, M., Gago, J., Molina, L., Duró, JC. (1998) Association between joint hypermobility syndrome and panic disorder. *American Journal of Psychiatry 155*: 1578-1583.

Mathias, CJ., Low, DA., Iodice, V., Owens, AP., Kirbis, M., Grahame, R. (2011) Postural tachycardia syndrome--current experience and concepts. *Nature Reviews Neurology 8*: 22-34.

McDonnell, NB., Gorman, BL., Mandel, KW., Schurman, SH., Assanah-Carroll, A., Mayer, SA., Najjar. SS., Francomano, CA. (2006) Echocardiographic findings in classical and hypermobile Ehlers-Danlos syndromes. *American Journal of Medical Genetics Part A 140*: 129-136.

Murray, B., Yashar, BM., Uhlmann, WR., Clauw, DJ., Petty, EM. (2013) Ehlers-Danlos syndrome, hypermobility type: A characterization of the patients' lived experience. *American Journal of Medical Genetics Part A 161A*: 2981-2988.

Ong, KT., Perdu, J., De Backer, J., Bozec, E., Collignon, P., Emmerich, J., Fauret, AL., Fiessinger, JN., Germain, DP., Georgesco, G., Hulot, JS., De Paepe, A., Plauchu, H., Jeunemaitre, X., Laurent, S., Boutouyrie, P. (2010) Effect of celiprolol on prevention of cardiovascular events in vascular Ehlers-Danlos syndrome: a prospective randomised, open, blinded-endpoints trial. *Lancet 376*: 1476-1484.

Pailhez, G., Rodríguez, A., Ariza, J., Palomo, AL., Bulbena, A. (2009) Somatotype and schizophrenia. A case-control study. *Actas Españolas de Psiquiatría 37*: 258-66.

Pailhez, G., Rosado, S., Baeza-Velasco, C., Bulbena, A. (2014) Ectomorphic somatotype and joint hypermobility are linked in panic and agoraphobic patients: a case-control study. *International Journal of Psychiatry in Clinical Practice 18*: 112-117.

Pailhez, G., Rosado, S., Bulbena Cabré, A., Bulbena, A. (2011) Joint hypermobility, fears, and chocolate consumption. *Journal of Nervous & Mental Disorders 199*: 903-906.

Pangarkar, S., Lee, PC. (2011) Conservative treatment for neck pain: medications, physical therapy, and exercise. *Physical Medicine & Rehabilitation Clinics of North America 22*: 503-520.

Pasquini, M., Celletti, C., Berardelli, I., Roselli, V., Mastroeni, S., Castori, M., Biondi, M., Camerota, F. (2014) Unexpected association between joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type and obsessive-compulsive personality disorder. *Rheumatology International 34*: 631-636.

Pepin, MG., Byers, PH. (2011) Ehlers-Danlos Syndrome Type IV. In: Pagon RA, Bird TD, Dolan CR, Stephens K, Adam MP (editors). *GeneReviews*™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016.

VOLUMEN 10. SPECIAL ISSUE 2016. DOI: 10.7714/CNPS/10.4.207

Rombaut, L., Scheper, M., De Wandele, I., De Vries, J., Meeus, M., Malfait, F., Engelbert, R., Calders, P. (2015) Chronic pain in patients with the hypermobility type of Ehlers-Danlos syndrome: evidence for generalized hyperalgesia. *Clinical Rheumatology 34*:1121-1129.

Rowe, PC., Barron, DF., Calkins, H., Maumenee, IH., Tong, PY., Geraghty, MT. (1999) Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome. *Journal of Pediatrics 135*: 494-499.

Sacheti, A., Szemere, J., Bernstein, B., Tafas, T., Schechter, N., Tsipouras, P. (1997) Chronic pain is a manifestation of the Ehlers-Danlos syndrome. *Journal of Pain & Symptom Management 14*: 88-93.

Shiari, R., Saeidifard, F., Zahed, G. (2013) Evaluation of the prevalence of joint laxity in children with attention deficit/ hyperactivity disorder. *Annals of Paediatric Rheumatology 3*: 78-80.

Sieg, KG. (1992) Autism and Ehlers-Danlos syndrome. *Journal of the American Academy of Child & Adolescent Psychiatry 31*: 173.

Smith, TO., Jerman, E., Easton, V., Bacon, H., Armon, K., Poland, F., Macgregor, AJ. (2013) Do people with benign joint hypermobility syndrome (BJHS) have reduced joint proprioception? A systematic review and meta-analysis. *Rheumatology International 33*: 2709-2716.

Steinmann, B., Royce, PM., Superti-Furga, A. (2002) The Ehlers-Danlos syndrome. In: Royce PM and Steinmann B, editors. *Connective tissue and its heritable disorders, 2nd edition*. New York (US):Wiley-Liss. 431-524.

Takei, A., Mera, K., Sato, Y., Haraoka, Y. (2011) High-functioning autistic disorder with Ehlers-Danlos syndrome. *Psychiatry & Clinical Neurosciences 65*: 605-606.

Tantam, D., Evered, C., Hersov, L. (1990) Asperger's syndrome and ligamentous laxity. *Journal of the American Academy of Child & Adolescent Psychiatry 29*: 892-896.

Tiller, GE., Cassidy, SB., Wensel, C., Wenstrup, RJ. (1998) Aortic root dilatation in Ehlers-Danlos syndrome types I, II and III. A report of five cases. *Clinical Genetics 53*: 460-465.

Tinkle, BT., Bird, HA., Grahame, R., Lavallee, M., Levy, HP., Sillence, D. (2009) The lack of clinical distinction between the hypermobility type of Ehlers-Danlos syndrome and the joint hypermobility syndrome (a.k.a. hypermobility syndrome). *American Journal of Medical Genetics Part A 149A*: 2368-2370.

Vernon H, Humphreys BK. (2008) Chronic mechanical neck pain in adults treated by manual therapy: a systematic review of change scores in randomized controlled trials of a single session. *The Journal of Manual & Manipulative Therapy 16*: E42-52.

Voermans, NC., Knoop, H., Bleijenberg, G., van Engelen, BG. (2010a) Pain in Ehlers-Danlos syndrome is common, severe, and associated with functional impairment. *Journal of Pain & Symptom Management 40*: 370-378.

Voermans, NC., Knoop, H., van de Kamp, N., Hamel, BC., Bleijenberg, G., van Engelen, BG. (2010b) Fatigue is a frequent and clinically relevant problem in Ehlers-Danlos Syndrome. *Seminars in Arthritis & Rheumatism 40*: 267-274.

Voermans, NC., Knoop, H. (2011) Both pain and fatigue are important possible determinants of disability in patients with the Ehlers-Danlos syndrome hypermobility type. *Disability & Rehabilitation 33*: 706-707.

Wenstrup, RJ., Meyer, RA., Lyle, JS., Hoechstetter, L., Rose, PS., Levy, HP., Francomano, CA. (2002) Prevalence of aortic root dilation in the Ehlers-Danlos syndrome. *Genetics in Medicine 4*: 112-117.

VOLUMEN 10. SPECIAL ISSUE 2016. DOI: 10.7714/CNPS/10.4.207

Wiesmann, T., Castori, M., Malfait, F., Wulf, H. (2014) Recommendations for anesthesia and perioperative management in patients with Ehlers-Danlos syndrome(s). *Orphanet Journal of Rare Diseases 9*: 109.

Yeowell, HN., Steinmann, B. (2008) Ehlers-Danlos Syndrome, Kyphoscoliotic Form. In: Pagon RA, Bird TD, Dolan CR, Stephens K, Adam MP (editors). *GeneReviews*™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016.

Zarate, N., Farmer, AD., Grahame, R., Mohammed, SD., Knowles, CH., Scott, SM., Aziz, Q. (2010) Unexplained gastrointestinal symptoms and joint hypermobility: is connective tissue the missing link? *Neurogastroenterology & Motility 22*: 252-e78.

VOLUMEN 10. SPECIAL ISSUE 2016. DOI: 10.7714/CNPS/10.4.207