Research in Developmental Disabilities xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Research in Developmental Disabilities

Review article

A connective tissue disorder may underlie ESSENCE problems in childhood

Carolina Baeza-Velasco [a,*], Rodney Grahame [b], Jaime F. Bravo [c,d]

[a] Department of Psychology, Laboratory of Psychopathology and Health Process, University Paris Descartes – Sorbonne Paris Cité, Boulogne-Billancourt, France
[b] Division of Medicine, University College London, London, UK
[c] Medical School, University of Chile, Santiago, Chile
[d] Rheumatology Unit, San Juan de Dios Hospital, Santiago, Chile

ARTICLE INFO

Article history:
Received 19 May 2016
Received in revised form 24 October 2016
Accepted 25 October 2016
Available online xxx

Keywords:
ESSENCE
Joint hypermobility syndrome
Ehlers-Danlos syndrome
Neurodevelopmental disorders
Attention deficit
Hyperactivity
Hypoactivity
Developmental coordination disorder
Sleep problems
Feeding
A typical brain development

ABSTRACT

Background: Ehlers-Danlos syndrome hypermobility type, also known as Joint Hypermobility Syndrome (EDS-HT/JHS), is the most common hereditary disorder of the connective tissue (HDCT). It is characterized by tissue fragility, joint hypermobility and a wide range of articular and non-articular manifestations, which often appear in infancy. The clinical picture of EDS-HT/JHS is poorly known by the medical community, as is the presence of "ESSENCE" (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations) problems in affected children.
Aim: The present work reviews the clinical and empirical evidence for ESSENCE difficulties in children with EDS-HT/JHS.
Method: A narrative review of the literature was undertaken following a comprehensive search of scientific online databases and reference lists. This included publications of quantitative and qualitative research.
Results: Motor abnormality, hyperactivity/hypoactivity, inattention, speech/language, social interaction, behavioral, sleep, feeding and emotional problems are ESSENCE difficulties for which there is some evidence of an association with EDS-HT/JHS.
Conclusion: Children with EDS-HT/JHS present ESSENCE problems that often coexist and tend to be recognized before the HDCT. Clinicians encountering children with ESSENCE problems should consider the possibility of an underlying HDCT such as EDS-HT/JHS, probably influencing neurodevelopmental attributes in a subgroup of children. Awareness of these interconnected clinical problems might help improve early referral, diagnosis and treatment of EDS-HT/JHS.

Contents

* Corresponding author at: Laboratoire de Psychopathologie et Processus de Santé EA 4057, Institut de Psychologie, 71 Avenue Édouard Vaillant, 92100 Boulogne Billancourt, France.
E-mail address: carolina.baeza-velasco@parisdescartes.fr (C. Baeza-Velasco).

http://dx.doi.org/10.1016/j.ridd.2016.10.011
0891-4222/

What this paper adds

This work provides a comprehensive review of ESSENCE problems and neurodevelopmental disorders associated with EDS-HT/JHS. In this respect, this paper contributes to increasing awareness among clinicians of the importance of considering a hereditary disorder of the connective tissue underlying ESSENCE problems in children, especially when there is a family history of similar difficulties, pain or joint hypermobility. In addition, this work contributes suggestions for research in an emerging area, combining somatic and developmental/psychiatric aspects.

1. Introduction

Heritable Disorders of Connective Tissue (HDCT) is a group of genetic disorders affecting the matrix of connective tissue proteins (collagens, elastins, fibrillins and tenascins) (Grahame & Hakim, 2006). HDCT are characterized by tissue fragility and joint hypermobility (JH), an inherited trait in which the joints have a range of motion beyond normal limits. JH is very common in the general population with a reported prevalence of 6.7–43% in children, adolescents and young adults with variations depending on age, ethnicity and the assessment method (Hakim & Grahame, 2003; Maillard & Murray, 2003; Mulvey et al., 2013). JH alone is not a medical problem. However, when it is associated with other physical complaints, it should alert health professionals to the presence of HDCT (Hakim, Malfait, & De Paepe, 2010), which include pathologies such as Marfan syndrome, Osteogenesis Imperfecta and Ehlers-Danlos syndrome (EDS). Concerning EDS, several subtypes have been described by geneticists (Beighton, De Paepe, Steinmann, Tsipouras, & Wenstrup, 1998), which range from mild to life-threatening (see Table 1 for a classification of EDS syndromes). The most common form of EDS is the hypermobility type (EDS-HT), which overlaps with the rheumatologic clinical condition named Joint Hypermobility Syndrome (JHS), considered one of the most frequent disorders in rheumatologic clinical practice, especially in women (Bravo & Wolff, 2006; Grahame, 2008). EDS-HT and JHS have been considered clinically indistinguishable (Tinkle et al., 2009). Thus, in the recent literature, both overlapping connective tissue disorders are referred to with the acronym EDS-HT/JHS. The prevalence of EDS-HT/JHS is estimated to be in the region of 3% (Hakim & Grahame, 2014).

According to Castori, 2012 in most EDS subtypes, "mutations in genes encoding collagen chains or proteins involved in their biogenesis" have been identified. Thus, for these subtypes (e.g. vascular, classic, and kyphoscoliotic forms), the diagnosis can be confirmed through molecular and biochemical procedures (Callewaert, Malfait, Loeys, & De Paepe, 2008). This is not the case for EDS-HT/JHS, in which the genetic defects remain unclear (Castori 2012), although there is some slight evidence linking TNXB and COL3A1 mutations to EDS-HT (Narcisi, Richards, Ferguson, & Pope, 1994; Schalkwijk et al., 2001; Zweers et al., 2003). In this sense, the clinical overlap between the genetic collagen disorders and EDS-HT/JHS appears as "strong presumptive evidence that this syndrome is, indeed, a member of the HDCT group of diseases" (Grahame, 1999). Hence, the diagnosis of EDS-HT/JHS is clinical. Two sets of diagnostic criteria are currently used: Villefranche for EDS-HT (Beighton et al., 1998) (Table 1) and Brighton for JHS (Grahame, Bird, & Child, 2000) (Table 2). Both sets need the preliminary assessment of JH. In this regard, the Beighton score (Beighton, Solomon, & Soskolne, 1973) is the most used in clinical and research settings to evaluate the widespread nature of JH (Grahame & Hakim, 2013) in adults and pediatric populations. The Beighton score requires the performance of 5 maneuvers: four passive bilateral and one active unilateral performance (Fig. 1), with a maximum score of nine points. In adults, the presence of JH is considered if an individual presents 4 out of 9 points. Because children have a range of motion greater than adults (Adib, Davies, Grahame, Woo, & Murray, 2005), a Beighton score of at least 5 out of 9 is recommended to identify JH (Romeo et al., 2016; Scheper et al., 2013).

Beyond the symptoms explored by these official diagnostic tools, other manifestations evidenced by recent research must be taken into account. These include multisystemic problems that usually appear in childhood (Castori, Sperduti, Celleti, Camerota, & Grammatico, 2011). The wider clinical spectrum of EDS-HT/JHS comprising symptoms in multiple body systems (Colombi, Dordoni, Chiarelli, & Ritelli, 2015; Hamonet et al., 2014) is presented in Table 3. Such multifaceted symptomatology can be understood by the wide distribution of collagen in the body. According to Castori et al. (2013), the features of EDS-HT/JHS are age-dependent and in the first decade, namely the first disease phase, the main symptoms are osteoarticular

Please cite this article in press as: Baeza-Velasco, C., et al. A connective tissue disorder may underlie ESSENCE problems in childhood. *Research in Developmental Disabilities* (2016), http://dx.doi.org/10.1016/j.ridd.2016.10.011

Table 1
The Villefranche classification of EDS syndromes (Beighton et al., 1998).

New Inheritance	Former	OMIM	
Classical type	Gravis (EDS type I)	130000	AD
	Mitis (EDS type II)	130010	AD
Hypermobility type	Hypermobility (EDS type III)	130020	AD
Major criteria : Hyperextensible and/or smooth, velvety skin, generalized joint hypermobility Minor criteria : Recurrent joint dislocation, chronic joint/limb pain, positive family history			
Vascular type	Arterial-ecchymotic I (EDS type IV)	130050 (225350) (225360)	AD
Kyphoscoliosis	Ocular-scoliotic (EDS type VI)	225400 (229200)	AR
Arthrochalasia type	Arthrochalasis multiplex congenita (EDS types VIIA and VIIB)	130060	ADy
Dermatosparaxis type	Human dermatosparaxis (EDS type VIIC)	225410	AR
Other forms	X-linked EDS (EDS type V)	305200	XL
	Periodontitis type (EDS type VIII)	130080	AD
	Fibronectin-deficient EDS (EDS type X)	225310	?
	Familial hypermobility syndrome (EDS type XI)	147900	AD
	Progeroid EDS	130070	?
	Unspecified forms	–	–

OMIM = Online Mendelian Inheritance in Man; AD = autosomal dominant; AR = autosomal recessive; XL = X-linked.

Table 2
Brighton Criteria for JHS (Grahame et al., 2000).

Major Criteria
1 A Beighton score of 4/9 or greater (either currently or historically)

- Arthralgia for longer than 3 months in 4 or more joints

Minor Criteria
1 A Beighton score of 1, 2 or 3/9 (0, 1, 2 or 3 if aged 50+)

- Arthralgia (>3 months) in one to three joints or back pain (>3 months), spondylosis, spondylolysis/spondylolisthesis.
- Dislocation/subluxation in more than one joint, or in one joint on more than one occasion.
- Soft tissue rheumatism .>3 lesions (e.g. epicondylitis, tenosynovitis, bursitis).
- Marfanoid habitus (tall, slim, span/height ratio >1.03, upper: lower segment ratio less than 0.89, arachnodactyly [positive S Steinberg/wrist signs].
- Abnormal skin: striae, hyperextensibility, thin skin, papyraceous scarring.
- Eye signs: drooping eyelids or myopia or antimongoloid slant.
- Varicose veins or hernia or uterine/rectal prolapse.

The JHS is diagnosed in the presence two major criteria, or one major and two minor criteria, or four minor criteria. Two minor criteria will suffice where there is an unequivocally affected first-degree relative.
JHS is excluded by presence of Marfan or Ehlers-Danlos syndromes (other than the EDS Hypermobility type). Criteria Major 1 and Minor 1 are mutually exclusive as are Major 2 and Minor 2.

JHS: Joint Hypermobility Syndrome.

(sprains, dislocations, joint clicking, growing pains, occasional back/joint pain), muscular (myalgias, cramps), sensorimotor (delayed attainment of motor skills, lack of coordination), visceral (constipation and/or diarrhea, bronchial hyper-reactivity, sensitivity to various foods such as gluten, under/hyperactive bladder), easy fatigability and headaches. In addition, Pacey et al. (2015) recently distinguished 5 subtypes of EDS-HT/JHS in children: the joint affected (high number of painful joints, recurrent joint instability episodes and orthostatic hypotension symptoms); the athletic (better muscle endurance, balance and leaping proficiency); the systemic (skin involvement and symptoms of urinary stress incontinence); the soft tissue affected (recurrent soft tissue damage and reduced hamstring muscle length); and high BMI (increased Body Mass Index centile for age).

This heterogenic (De Wandele et al., 2013), painful and potentially disabling chronic condition has been associated with poor quality of life in adults (Rombault, Malfait, Cools, De Paepe, & Calders, 2010) and children (Pacey, Tofts, Adams, Munns,

Please cite this article in press as: Baeza-Velasco, C., et al. A connective tissue disorder may underlie ESSENCE problems in childhood. *Research in Developmental Disabilities* (2016), http://dx.doi.org/10.1016/j.ridd.2016.10.011

Beighton score	Left side	Right side
1. Passively touch the forearm with the thumb, while flexing the wrist	1	1
2. Bend the little finger back to ≥ 90°	1	1
3. Hyperextension of the elbows greater than or equal to 10°	1	1
4. Knees hyperextension greater than or equal to 10°	1	1
5. Touching the floor with the palms of the hands when reaching down without bending the knees	1	
Total	/9	

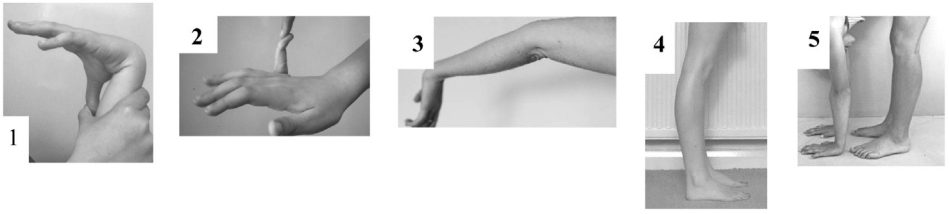

Fig. 1. Beighton score (Beighton et al., 1973).

Table 3
Clinical Spectrum of EDS-HT/JHS (Hamonet et al., 2014; Colombi et al., 2015).

Osteoarticular	i.e. mild scoliosis, flat foot, lumbar hyperlordosis, joint hypermobility
Muscular	i.e. hypotonia, fibromyalgia, recurrent myalgias and cramps, dystonia
Mucocutaneous	i.e. mildly hyperextensible skin, velvety/silky/soft skin texture, striae rubrae and/or distensae in young age, small or post-surgical atrophic scars, Keratosis pilaris, hernias, light blue sclerae, gingival inflammation/recessions, hypoplastic lingual frenulum, easy bruising, resistance to local anaesthetic drugs
Gastrointestinal	i.e. dysphagia, dysphonia, reflux gastroesophageal, gastritis, unexplained abdominal pain, food intolerances
Cardiovascular	i.e. varicose veins, low progressive aortic root dilatation, pseudo-Raynaud's phenomenon, mitral valve prolapse
Urogynaecological	i.e. dyspareunia, dysmenorrhea, urinary stress incontinence, meno/metrorrhagia.
Ocular	i.e. myopia, strabismus, palpebral ptosis.
Dental	i.e. dental neuralgia, gingivitis, temporo mandibular joint pain, dental pains to cold/warm.
Neuropsychiatric	i.e. dysautonomia, clumsiness, proprioceptive dysfunction, paresthesia, headache, fatigue, sleep disturbances, cognitive impairment, anxiety, hyperaesthesia, hyperosmia, hyperacousis.

& Nicholson, 2015). Unfortunately, there is a lack of awareness of the clinical presentation of EDS-HT/JHS among the medical community (Grahame & Bird, 2001; Russek, LaShomb, Ware, Wesner, & Westcott, 2016), and many patients have to cope with the burden of delayed diagnosis and misdiagnosis (Rombault et al., 2011). The manifestations that appear in infancy often remain overlooked until the appearance of widespread pain, sometimes decades later (Castori et al., 2013). In this regard, Adib et al. (2005) stated that in children, the diagnosis delay leads to poor control of pain and disruption of normal life at home and at school.

Some of the obstacles to EDS-HT/JHS recognition lie in the trivialization of signs and symptoms, the lack of consensus concerning the diagnostic criteria (Castori, 2012), the absence of recognizable disease markers (Colombi et al., 2015), the overlap with other clinical entities (Colombi et al. (2015)) and the fragmentation of care with increasing medical specialization (Goh & Shaw, 2007) to the detriment of the holistic approach necessary for EDS-HT/JHS recognition. Consequently, those affected are often neglected and misbelieved (Grahame, 2008, 2015).

1.1. EDS-HT/JHS and ESSENCE problems

In recent years, several authors have highlighted the strong association between EDS-HT/JHS and neurodevelopmental disorders (Baeza-Velasco, Pailhez, Bulbena, & Baghdadli, 2015a; Eccles et al., 2014; Ghibellini, Brancati, & Castori, 2015; Sinibaldi, Ursini, & Castori, 2015). Motor problems influenced by JH, balance problems, hypotonia and proprioception impairment (Maillard & Murray, 2003) are quite common in EDS-HT/JHS. Children affected are often described as clumsy, having poor balance and delayed toddling (Adib et al., 2005; Ghibellini et al., 2015; Maillard & Murray, 2003). They are also frequently considered overactive and inattentive and present other behavioral problems as well as emotional, social, and educational difficulties (Grahame, 2010). As Gillberg and Kadesjö (2003) stated, the co-occurrence of these problems with motor abnormality (e.g. motor delay, abnormal motor control) is more the norm than the exception, and this is the reality for a significant number of children with EDS-HT/JHS. Thus, because of the disregarded status of EDS-HT/JHS, many affected children accumulate several inconclusive medical explorations resulting in multiple diagnostic categorizations (Ghibellini et al., 2015) before the identification of EDS-HT/JHS. Many of these diagnoses are psychiatric/psychological (e.g. Developmental Coordination Disorder: DCD; Attention Deficit Hyperactivity Disorder: ADHD). As a result, child psychiatry/neurology professionals are often in contact with this population before the specialists of EDS-HT/JHS. This is not surprising considering that parents having difficulty in dealing with behavioral problems (sometimes influenced by pain in EDS-HT/JHS) are motivated to seek

Please cite this article in press as: Baeza-Velasco, C., et al. A connective tissue disorder may underlie ESSENCE problems in childhood. *Research in Developmental Disabilities* (2016), http://dx.doi.org/10.1016/j.ridd.2016.10.011

early professional help in the psychiatric field. In addition, although tissue fragility and JH might be perceived early, the onset (or recognition) of EDS-HT/JHS complaints/symptoms might occur after the appearance of motor and behavioral problems, probably when the child has acquired sufficient language skills to formulate complaints related to pain. For example, Adib et al. (2005) observed in a group of children with EDS-HT/JHS in the UK that the mean age at onset of symptoms was 6.2 years, while the diagnostic average age was 9 years, thus confirming a significant diagnostic delay.

The acronym ESSENCE stands for Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations. This was proposed by Gillberg (2010) to stress the need to explore clusters of neurodevelopmental problems in the first 5 years of life, which are often screened separately resulting in discrete diagnoses (e.g. ADHD, DCD) despite the fact that they are highly coexisting. These problems occur in the fields of general development, communication and language, social interrelatedness, motor coordination, attention, activity, behavior, mood, sleep and feeding (Gillberg, 2010). As stated above, ESSENCE problems are present in a significant number of children with EDS-HT/JHS. Thus, the ESSENCE framework seems useful to apply systematically to EDS-HT/JHS. In addition, practitioners working with children with ESSENCE problems (e.g. child psychiatrists, psychologists, and neurologists) should consider the possibility of an underlying connective tissue disorder, probably influencing neurodevelopmental problems in a subgroup of individuals. In this sense, it has been stated that hereditary factors play a role in the development of ESSENCE problems. Gillberg, Rasmussen, Carlström, Svenson, & Waldenström (1982), and Landgrem, Kjellman, and Gillberg (1998) highlighted that in one third of children with motor, attention and perceptual problems, family factors (e.g. family motor clumsiness, family language disorder) constitute the main clue to their etiology (Gillberg & Kadesjö, 2003).

Otherwise, the variability and comorbidity among neurodevelopmental and ESSENCE problems has been attributed to a more general deficit, the so-called "atypical brain development". This is a concept describing "the developmental variation of the brain and brain-based skills on either side of the real or hypothetical norm" (Gilger & Kaplan, 2001) as a result of genetics and/or environmental factors, and accounting for all atypicalities including impairments as well as exceptional skills in specific domains. Interestingly, beyond the plethora of impairments presented by people with EDS-HT/JHS mentioned above, it is not uncommon to observe in clinical practice the description of high abilities (e.g. music, sport, academic performance) (Hamonet, Ducret, Layadi, & Baeza-Velasco, 2016), coexisting with these impairments or presented before the onset of pain and other problems associated with EDS-HT/JHS. In addition, although studies in brain imaging in people with hypermobility-related conditions are scarce, recent works have evidenced some particular features worth mentioning. Recently, Mallorqui-Bagué et al. (2014), in their functional neuroimaging study comparing people with and without JH, observed an enhanced neural reactivity to sad and angry scenes within brain regions related to states of anxiety (insular cortex). Meanwhile, Eccles et al. (2012) found structural differences between hypermobile and non-hypermobile participants in brain areas involved in emotion processing, attention, cognitive control of pain, and negative emotions (bilateral amygdala, anterior cingulate, parietal lobe), as well as a negative correlation between the degree of JH and the superior temporal volume, which is an area related to processing social and emotional signals. For these authors "processes compromising function in neurodevelopmental conditions may occur in individuals with JH", which may favor psychiatric vulnerability (Eccles et al., 2012). As Tantam et al. (1990) suggested, abnormalities in brain structure or atypical brain development due to connective tissue abnormality may help explain developmental delays and ESSENCE problems in individuals with HDCT.

The aim of the present study was to conduct a narrative review of the clinical and empirical evidence for ESSENCE difficulties in children with EDS-HT/JHS.

2. Method

A comprehensive search of electronic databases (PubMed, psycINFO, ScienceDirect, and Q-Sensei Scholar) was conducted including publications based on quantitative and qualitative research and case reports. The terms searched for were "joint hypermobility", "Ehlers-Danlos syndrome", "heritable disorders of connective tissue" combined with "children", "neurodevelopmental disorders", "mental disorders", "sleep", "language", "distress", "eating", "behavior", "hyperactivity", "attention deficit", "motor problems", "ESSENCE", and "atypical brain development". The articles identified in this first step were further scrutinized for additional references. Our search included studies published from 1973 until August 2016, with no exclusion based on the language of publication.

3. Results

One hundred and four articles were included in this review. The information was regrouped according to the ESSENCE symptom domains proposed by Gillberg (2010). These are motor abnormality, speech and language problems, hyperactivity/inattention, hypoactivity, social interaction/communication and behavior problems, sleep problems, feeding difficulties and emotional problems.

3.1. Motor abnormality

An association between JH and early motor delay was reported by Jaffe, Tirosh, and Cohen (1988). Later, the same group compared 18-month-old hypermobile children (n = 59) with and without motor delay in terms of their motor function at the age of 5. Their results showed that those with motor delay had significantly worse gross and fine motor performances

Please cite this article in press as: Baeza-Velasco, C., et al. A connective tissue disorder may underlie ESSENCE problems in childhood. *Research in Developmental Disabilities* (2016), http://dx.doi.org/10.1016/j.ridd.2016.10.011

than those hypermobile children without motor delay, thus identifying a subgroup of patients susceptible to having poor motor outcomes (Tirosh, Jaffe, Marmur, Taub, & Rosenberg, 1991). Engelbert et al. (2005) observed a severe delay in motor development in a third of children with JH (n = 72).

Adib et al. (2005) studied 125 children with EDS-HT/JHS and found that 48% were described as clumsy, 36% as having poor coordination and 10% as having an abnormal gait. Kirby and Sugden (2007) reported that symptoms of EDS-HT/JHS were significantly more common in children with DCD than in children with typical development (n = 27 for each group). These authors stressed the overlap between DCD and EDS-HT/JHS. In fact, the American Psychiatric Association has added JHS in the differential diagnosis of DCD (Baeza-Velasco, Pailhez et al., 2015) in the Statistical Manual of Mental Disorders, 5th edition (DSM-5; American Psychiatric Association, 2013). The work of Easton et al. (2014) with 119 children with EDS-HT/JHS (5–16 years) showed that 18.4% had significant movement difficulty as assessed by the Movement Assessment Battery for Children 2 (Henderson, Sudgen, & Barnett, 2007).

Recently, Celletti et al. (2015) explored the prevalence of JH with the Beighton score in children with DCD (n = 41). Forty six percent of children (n = 19) were identified as hypermobile, confirming the high prevalence of JH in DCD. Compared to DCD without JH, these hypermobile children had significantly more frequent falls (95% vs. 18%) and motor impersistence or the inability to maintain a fixed posture (89% vs. 23%). According to Ghibellini et al., 2015, the hypermobile individuals who develop DCD are probably those with an impairment of proprioception.

3.2. Speech and language problems

Hunter, Morgan, and Bird (1998) first reported a high level of speech and language problems in 157 out of 327 pre- and school-age children with EDS (different subtypes). Adib et al. (2005) observed in a cohort of 125 children with EDS-HT/JHS that 13% had speech problems and 14% learning difficulties, as assessed by the Linguistic Comprehension Test (LCT) (Rustioni, 1994). Celletti et al. (2015) explored the prevalence of JH in children with DCD (n = 41). They observed that those with JH (46%) had significantly more narrative difficulties than children with DCD without JH. These authors suggested that narrative and motor difficulties in children with JH or EDS-HT/JHS might share a common pathogenesis. In addition, Rimmer et al. (2008) reported dysphonia from birth in two children with EDS. Thus, a connective tissue disorder might underlie speech problems (e.g. low muscle tone, hypermobility of oral structures) (Celletti et al., 2015; Rimmer, Giddings, Cavalli, & Hartley, 2008).

3.3. Hyperactivity/Inattention

Harris (1998), working with individuals with ADHD, first reported the high occurrence of JH among them. From his clinical observations, he estimated that 99% of a cohort of 200 individuals were hypermobile. The method to asses JH was not reported. More recently, two control-case studies confirmed a significantly higher frequency of JH in children with ADHD compared to controls. The first, by Koldas Dogan, Taner, and Evcik (2011), observed that 31.5% of those with ADHD (n = 54) had a positive Beighton score, compared to only 13.9% of their healthy counterparts. In the second study, by Shiari, Saeidifard, and Zahed (2013), the prevalence of JH in children with ADHD was 74.4% versus 12.8% in controls (n = 86 in both groups).

Concerning EDS, Grahame (2010) stated that children with EDS-HT/JHS present an irrepressible fidgetiness. In this sense, Hollertz (2003, 2012) speculated about a common biological base shared by ADHD and EDS after observing the frequent co-occurrence of both pathologies in a clinical setting. A study of 23 Italian individuals with EDS-HT/JHS revealed that 8 of them (34.8%) also had ADHD (Castori et al., 2014). Hershenfeld et al. (2016) reported a high prevalence of psychiatric disorders among adults with EDS, in whom 6 out of 72 with the hypermobile type (8.3%) had ADHD (J. So, personal communication, November 23, 2015). This figure is much higher than the prevalence observed in the general population (2.5%) (Simon, Czobor, Bálint, Mészáros, & Bitter, 2009). Recently, Cederlöf, Larsson, Lichtenstein, Almqvist, and Serlachius Ludvigsson (2016) in a nationwide population-based cohort of people with EDS and JHS (n = 1.771), observed that EDS (different subtypes) was associated with ADHD (risk ratio = 5.6; 95% confidence interval = 4.2–7.4).

3.4. Hypoactivity

Unfitness and poor stamina are common in children with EDS-HT/JHS. Thus, a decrease in activity can be observed in children with EDS-HT/JHS as a consequence of pain. In other words, the intrinsic tendency to suffer trauma due to tissue fragility leads to pain, which in turn leads to inactivity and rest resulting in muscle weakness and reduced stamina (Maillard & Murray, 2003). Another clue to understanding hypoactivity in EDS-HT/JHS is the alteration in the autonomic nervous system, or dysautonomia, related to this syndrome (Bravo & Wolff, 2006) due to the presence of vasovagal dystonia and a failure of collagen tissue in the wall of the venous capillaries, which contributes to the drop in blood pressure (Bravo, 2012). According to Bravo (Bravo, 2012, 2015), dysautonomia leads to chronic fatigue/sleepiness (e.g. when the patient is inactive or after a heavy meal) and the feeling of having no energy. Thus, it is not uncommon for these people to be labeled as lazy or unsociable (Bravo, 2015), or having a low mood or depression. These observations are consistent with those of Bulbena et al. (2015), who recently proposed the "neuroconnective phenotype" model to describe somatic and psychological features often seen in people with JH and anxiety. The behavioral dimension of the model includes "patterns of defensive mechanisms that are often identifiable at the extreme of a continuous axis" (Bulbena, Pailhez, Bulbena-Cabré, Mallorqui-Bagué, & Baeza-Velasco,

Please cite this article in press as: Baeza-Velasco, C., et al. A connective tissue disorder may underlie ESSENCE problems in childhood. *Research in Developmental Disabilities* (2016), http://dx.doi.org/10.1016/j.ridd.2016.10.011

2015), such as ergotropic behaviors with increased activity and hypervisibility (as seen in the "hyperactive" part), but also trophotropic behaviors with sleep, social withdrawal and rest, as well as a restriction of activities and delayed use of time.

3.5. Social interaction/communication and behavior problems

These aspects of EDS-HT/JHS have not yet been studied systematically; however some reports mention difficulties in this area. The work of Lumley, Jordan, Rubenstein, Tsipouras, and Evans (1994), with 7 children with EDS (various subtypes) aged from 6 to 12 years, explored social competences and behavioral problems using the Child Behavior Checklist (Achenbach & Edelbrock, 1983). Their results showed that only 2 children were typical from a psychiatric point of view. Four of them had impaired social competence. Three showed internalizing problems, such as anxiety/depression and withdrawal, one exhibited a very aggressive behavior and the other presented behavioral problems not detailed. Moreover, pain, which is one of the most frequent symptoms reported in EDS-HT/JHS (Hamonet et al., 2014), has been associated with behavioral problems in children (Varni et al., 1996).

In addition, EDS-HT/JHS, in which motor problems are common, might represent a vulnerable population concerning deficits in social abilities. Coordination and motor skills are necessary for the development of social competences (Bejerot, 2011), and poor motor coordination has been recognized as a factor negatively affecting social and emotional functioning in children of school age (Piek, Bradbury, Elsley, & Tate, 2008). Activities and games in infancy require motor abilities and difficulties in the motor sphere, like those observed in DCD, limit participation in these activities leading to a negative impact on social behavior and peer relationships with the risk of social exclusion (Leonard, 2016). According to Schoemaker and Kalverboer (1994), compared to children without movement problems, those who are clumsy are more introverted and anxious, and judge themselves as less physically and socially competent. In this context, bullying experiences have been related to motor problems and suggest a deficit in social competences (Bejerot, Edgar, & Humble, 2010), while people with EDS-HT/JHS frequently report having been bullied at school (Baeza-Velasco, Bulbena, Pailhez, Bourdon, & De Jouvencel, 2016).

It is worth mentioning that some case reports have linked EDS and autism spectrum disorders (Baeza-Velasco et al. (2016c); Fehlow & Tennstedt, 1985; Sieg, 1992; Takei, Mera, Sato, & Haraoka, 2011; Tantam, Evered, & Hersov, 1990). In addition, JH has been found to be more prevalent among children with autism compared to their typical counterparts (Shetreat-Klein, Shinnar, & Rapin, 2014). The work by Cederlöf et al. (2016) found that individuals with EDS and JHS (n = 1.771) are at increased risk of being diagnosed with autism spectrum disorders (risk ratio = 7.4; 95% confidence interval = 5.2–10.7). According to Tantam et al. (1990), an alteration in connective tissue might lead to brain structural abnormalities or motor developmental delay, which in turn could negatively impact non-verbal social abilities as well as emotion expression.

3.6. Sleep problems

Although current knowledge concerning the specific characteristics of sleep disorders in EDS, and more specifically in people with EDS-HT/JHS, is poor (Metlaine, 2016), there is evidence for a high frequency of sleep problems in this population. Verbraecken, Declerck, Van den Heyning, De Backer, and Wouters (2001) studied 9 individuals with EDS of whom 56% reported disturbed maintenance of sleep, which was related to poor quality of life. Voermans, Knoop, Bleijenberg, and van Engelen (2010) explored pain and sleep disturbances in people with EDS (n = 273). In this study, they found that people with the hypermobility type (EDS-HT/JHS) had more severe pain than those with the classic type of EDS. In addition, a correlation was observed between pain and low nocturnal sleep quality. A similar observation was reported by Hamonet et al. (2014) who stated that 40% of individuals with EDS complained about sleep problems. Painful awakening and poor sleep seem related to positional discomfort and proprioceptive alterations (Hamonet et al., 2014). In addition, Guilleminault et al. (2013) reported abnormal breathing during sleep in people with EDS, which led to fatigue and poor sleep.

Moreover, beyond pain, other extra-articular manifestations reported in children with EDS-HT/JHS, such as enuresis (Adib et al., 2005), might contribute to sleep problems. For example, girls with generalized JH have been shown to present more nighttime urinary incontinence than controls (De Kort, Verhulst, Engelbert, Uiterwaal, & de Jong, 2003) as well as a high level of stress incontinence symptoms (Pacey et al., 2015).

3.7. Feeding difficulties

Certain functional problems linked to EDS-HT/JHS may lead to an inability or a refusal to eat certain foods. Oropharyngeal dysphagia is common in those affected. This can contribute to feeding problems, and may lead to a failure to thrive in children (Castori, 2012). Recently, Celletti et al. (2015) observed that children with DCD and JH showed a greater occurrence of atypical swallowing than children with DCD without JH. In addition, problems that are common in EDS-HT/JHS, such as gastrointestinal (e.g. abdominal pain, reflux, constipation) and temporomandibular disorders, fragility of oral mucosa, dental problems, and smell and taste alterations, can lead to difficult/painful eating and negatively impact food acceptability (Baeza-Velasco, Van den Bossche, Grossin, & Hamonet, 2016b). Interestingly, JH has also been associated with underweight and malnutrition in children (Hasija, Khubchandani, & Shenoi, 2008; Sanjay, Bagalkoti, & Kubasadgoudar, 2013).

Please cite this article in press as: Baeza-Velasco, C., et al. A connective tissue disorder may underlie ESSENCE problems in childhood. *Research in Developmental Disabilities* (2016), http://dx.doi.org/10.1016/j.ridd.2016.10.011

3.8. Emotional problems

Concerning mood, several studies have shown high levels of psychological distress in adults with EDS-HT/JHS. However, there is a lack of studies regarding these aspects in children (Smith et al., 2014). The link between JH and pathological anxiety has solid empirical support (Pailhez & Bulbena, 2013). Among factors influencing this association are a possible shared genetic base (Gratacos et al., 2001), particular structural brain features in areas related to emotion regulation observed in people with JH (Eccles et al., 2012), the autonomic dysfunction seen in EDS-HT/JHS in which symptoms overlap with those of anxiety disorders (e.g. palpitations, tremors, breathlessness, etc.), and the interpretation of physiological states of the body that influence the development of anxiety states (Clark, 1986; Craig, 2003; Damasio, 1996). In this regard, interoception (Mallorqui-Bagué et al., 2014) and somatosensory amplification (Baeza-Velasco, Gély-Nargeot, Bulbena, Fénétrier, & Bravo, 2011) have been reported as being increased in JH and EDS-HT/JHS. In addition, distressed mood has been found to be significant among children with chronic pain (Eccleston et al., 2012) and adolescents with poor motor competence (Rigoli, Piek, & Kane, 2012). Further studies are needed to explore whether this is the case for EDS-HT/JHS in pediatric populations.

4. Conclusion

Emerging research highlights a plethora of problems linked to EDS-HT/JHS, in which neurodevelopmental disturbances and/or ESSENCE problems, such as motor abnormality, hyper/hypoactivity, inattention, language, social interaction, behavioral, sleep, mood and feeding difficulties, are common and may constitute a clue to an underlying HDCT in pediatric populations.

In this regard, and considering the hereditary nature of EDS-HT/JHS, the presence of ESSENCE problems when there is a family history of similar difficulties, JH and/or painful conditions should lead to this common connective tissue disorder being suspected and screened. Thus, there is a real need to increase awareness about the clinical presentation of EDS-HT/JHS among child health practitioners (Baeza-Velasco, Soussana, & Baghdadli, 2015b), especially those working in child psychiatric services and encountering children with ESSENCE problems, in order to ensure early referral to specialized centers. A worsening of symptoms in adulthood, as seen in the natural progression of EDS-HT/JHS (Castori et al., 2013), could be prevented to some degree by a prompt diagnosis and treatment, which are currently significantly delayed worldwide.

The ESSENCE framework is useful in EDS-HT/JHS conceptualization because it illustrates the clinical reality of people with EDS-HT/JHS presenting with an assortment of coexisting developmental difficulties, which are often screened separately so that concomitant problems are overlooked, and treated by one type of (or few) health professional(s), when a multidisciplinary management is needed (Gillberg et al., 1982; Plenty, Heurlin, Arlinde, & Bejerot, 2013). In this context of ESSENCE presentation, considering the involvement of connective tissues might help, on one hand, to explain the atypical brain development suggested by the variability and comorbidity of developmental problems and, on the other hand, to identify a group of children who are highly vulnerable from a psychological and physical point of view, such as those affected with EDS-HT/JHS.

Compliance with ethical standards

The manuscript does not contain clinical studies or patient data. The author declares no conflict of interest and does not have any financial.

disclosures.

Conflict of interest

The author has no conflict of interest to disclose.

Informed consent statement

The manuscript does not contain clinical studies or patient data, thus approval by an ethics committee and informed consent were not applicable.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

Achenbach, T. M., & Edelbrock, C. S. (1983). *Manual for the child behavior checklist and revised child behavior profile*. Burlington, VT: University Associates in Psychiatry.

Adib, N., Davies, K., Grahame, R., Woo, P., & Murray, K. J. (2005). Joint hypermobility syndrome in childhood. A not so bening multisystem disorder? *Rheumatology*, *44*, 744–750.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington; VA: American Psychiatric Publishing.

Please cite this article in press as: Baeza-Velasco, C., et al. A connective tissue disorder may underlie ESSENCE problems in childhood. *Research in Developmental Disabilities* (2016), http://dx.doi.org/10.1016/j.ridd.2016.10.011

Baeza-Velasco, C., Gély-Nargeot, M. C., Bulbena, A., Fénétrier, C., & Bravo, J. F. (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., Pailhez, G., Bulbena, A., & Baghdadli, A. (2015). Joint hypermobility and the heritable disorders of connective tissue: Clinical and empirical evidence of links with psychiatry. *General Hospital Psychiatry*, *37*, 24–30. http://dx.doi.org/10.1016/j.genhosppsych.2014.10.002
Baeza-Velasco, C., Soussana, M., & Baghdadli, A. (2015). Connective tissue problems and attention deficit and hyperactivity. *Attention Deficit and Hyperactivity Disorders*, *7*, 177–178. http://dx.doi.org/10.1007/s12402-014-0161-y
Baeza-Velasco, C., Bulbena, A., Pailhez, G., Bourdon, C., & De Jouvencel, M. (2016). Syndrome d'Ehlers-Danlos hypermobile: Considérations psychologiques. *Journal De Réadaptation Médicale*, *36*, 78–84. http://dx.doi.org/10.1016/j.jrm.2015.09.004
Baeza-Velasco, C., Van den Bossche, T., Grossin, D., & Hamonet, C. (2016). Eating difficulties and significant weight loss in joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type. *Eating and Weight Disorders*, *21*, 175–183. http://dx.doi.org/10.1007/s40519-015-0232-x
Baeza-Velasco, C., Hamonet, C., Baghdadli, A., & Brissot, R. (2016). Autism spectrum disorders and Ehlers-Danlos syndrome hypermobility-type: Similarities in clinical presentation. *Cuadernos De Medicina Psicosomatica Y Psiquiatria De Enlace*, *118*, 49–58.
Beighton, P., Solomon, L., & Soskolne, C. (1973). Articular mobility in an African population. *Annals of the Rheumatic Diseases*, *32*, 413Y8.
Beighton, P., De Paepe, A., Steinmann, B., Tsipouras, P., & Wenstrup, R. J. (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.
Bejerot, S., Edgar, J., & Humble, M. B. (2010). Poor performance in physical education −A risk factor for bully victimization. A case control study. *Acta Pediatrica*, *100*, 413–439. http://dx.doi.org/10.1111/j.1651-2227.2010.02016.x
Bejerot, S. (2011). The relationship between poor motor skills and neurodevelopmental disorders. *Developmental Medicine & Child Neurology*, *53*, 779. http://dx.doi.org/10.1111/j.1469-8749.2011.04041.x
Bravo, J. F., & Wolff, C. (2006). Clinical study of hereditary disorders of connective tissues in a Chilean population. Joint Hypermobility Syndrome and vascular Ehlers-Danlos syndrome. *Arthritis & Rheumatology*, *54*, 515–523.
Bravo, J. F. (2012). Dificultades en el diagnostico y tratamiento de la disautonomia. *Revista Chilena De Reumatologia*, *28*, 152–158.
Bravo, J. F. (2015). Dysautonomia in Ehlers-Danlos type III. In *Conference at the International colloquium The treatments of Ehlers-Danlos syndrome*.
Bulbena, A., Pailhez, G., Bulbena-Cabré, A., Mallorqui-Bagué, N., & Baeza-Velasco, C. (2015). Joint hypermobility, anxiety and psychosomatics: Two and a half decades of progress toward a new phenotype. *Advances in Psychosomatic Medicine*, *34*, 143–157. http://dx.doi.org/10.1159/000369113
Callewaert, B., Malfait, F., Loeys, B., & De Paepe, A. (2008). Ehlers-Danlos syndrome and Marfan syndrome. *Best Practice & Research: Clinical Rheumatology*, *22*, 165–189. http://dx.doi.org/10.1016/j.berh.2007.12.005
Castori, M., Sperduti, I., Celleti, C., Camerota, F., & Grammatico, P. (2011). Symptom and joint mobility progression in the joint hypermobility syndrome (Ehlers-Danlos syndrome, hypermobility type). *Clinical and Experimental Rheumatology*, *29*, 998–1005.
Castori, M., Morlino, S., Celleti, C., Ghibellini, G., Bruschini, M., Grammatico, P., et al. (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*, *161A*(Part A), 2989–3004. http://dx.doi.org/10.1002/ajmg.a.36315
Castori, M., Dordoni, C., Valiante, M., Sperduti, I., Ritelli, M., Morlino, S., et al. (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*, *164A*(Part A), 3010–3020. http://dx.doi.org/10.1002/ajmg.a.36805
Castori, M. (2012). Ehlers-Danlos syndrome, hypermobility type: An underdiagnosed hereditary connective tissue disorder with mucocutaneous, articular, and systemic manifestations. *ISRN Dermatology*, *751768* http://dx.doi.org/10.5402/2012/751768
Cederlöf, M., Larsson, H., Lichtenstein, P., Almqvist, C., & Serlachius Ludvigsson, J. F. (2016). Nationwide population-based cohort study of psychiatric disorders in individuals with Ehlers-Danlos syndrome or hypermobility syndrome and their syblings. *BMC Psychiatry*, *16*(207) http://dx.doi.org/10.1186/s12888-016-0922-6
Celletti, C., Mari, G., Ghibellini, G., Celli, M., Castori, M., & Camerota, F. (2015). Phenotypic variability in developmental coordination disorder: Clustering of generalized joint hypermobility with attention deficit/hyperactivity disorder, atypical swallowing and narrative difficulties. *American Journal of Medical Genetics*, *169C (1*(Part C), 117–122. http://dx.doi.org/10.1002/ajmg.c.31427
Clark, D. M. (1986). A cognitive approach to panic. *Behaviour Research and Therapy*, *24*, 461–470.
Colombi, M., Dordoni, C., Chiarelli, N., & Ritelli, M. (2015). Differential diagnosis and diagnostic flow chart of joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type compared to other heritable connective tissue disorders. *American Journal of Medical Genetics*, *169C*, 6–22. http://dx.doi.org/10.1002/ajmg.c.31429
Craig, A. D. (2003). Interoception: The sense of the physiological conditoin of the body. *Current Opinion in Neurobiology*, *13*, 500–505.
Damasio, A. R. (1996). The somatic marker hypothesis and the possible functions of prefrontal cortex. *Philosophical Transactions of the Royal Society of London Series B Biological Sciences*, *351*, 1413–1420.
De Kort, L. M., Verhulst, J. A., Engelbert, R. H., Uiterwaal, C. S., & de Jong, T. P. (2003). Lower urinary tract dysfonction in children with generalized hypermobility of joints. *Journal of Urology*, *170*, 1971–1974.
De Wandele, I., Rombault, L., Malfait, F., De Backer, T., De Paepe, A., & Calders, P. (2013). Clinical heterogeneity in patients with the hypermobility type of Ehlers-Danlos syndrome. *Research in Developmental Disabilities*, *34*, 873–881. http://dx.doi.org/10.1016/j.ridd.2012.11.018
Easton, V., Bale, P., Bacon, H., Jerman, E., Armon, K., & Macgregor, A. J. (2014). The relationship between bening joint hypermobility syndrome and developmental coordination disorders in children. *Arthritis & Rheumathology*, *66*, S124. http://dx.doi.org/10.1002/art.38505
Eccles, J. A., Beacher, F. D., Gray, M. A., Jones, C. L., Minati, L., Harrison, N. A., et al. (2012). Brain structure and joint hypermobility: Relevance to the expression of psychiatric symptoms. *British Journal of Psychiatry*, *200*, 508–509. http://dx.doi.org/10.1192/bjp.bp.111.092460
Eccles, J. A., Iodice, V., Dowell, N. G., Owens, A., Hughes, L., Skipper, S., et al. (2014). Joint hypermobility and autonomic hyperactivity: Relevance to neurodevelopmental disorders. *Journal of Neurology, Neurosurgery & Psychiatry*, *85*(e3) http://dx.doi.org/10.1136/jnnp-2014-308883.9
Eccleston, C., Palermo, T. M., Williams, A., Lewandowski, A., Mormey, S., Fisher, E., et al. (2012). Psychological therapies for the management of chronic and current pain in children and adolescents. *Cochrane Databased of Systematic Review*, *12*(12), CD003968. http://dx.doi.org/10.1002/14651858.CD003968.pub3
Engelbert, R. H., Kooijmans, F. T., van Riet, A. M., Feitsma, T. M., Uiterwaal, C. S., & Helders, P. J. (2005). The relationship between generalized joint hypermobility and motor development. *Pediatric Physical Therapy*, *17*, 258–263.
Fehlow, P., & Tennstedt, A. (1985). Concomitant neuropsychiatric symptoms in a case of Ehlers–Danlos syndrome. *Psychiatrie, Neurologie und Medizinische Psychologie (Leipz)*, *37*, 215–220.
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*, *999*, 1–10. http://dx.doi.org/10.1002/ajmg.c.31424
Gilger, J. W., & Kaplan, B. J. (2001). Atypical brain development: A conceptual framework for understanding developmental learning disabilities. *Developmental Neuropsychology*, *20*, 465–481.
Gillberg, C., & Kadesjö, B. (2003). Why bother about clumsiness? The implications of having developmental coordination disorder (DCD). *Neural Plasticity*, *10*, 59–68.
Gillberg, C., Rasmussen, P., Carlström, G., Svenson, B., & Waldenström, E. (1982). Perceptual, motor and attentional deficits in six-years-old children. Epidemiological aspects. *Journal of Child Psychology and Psychiatry*, *23*, 131–144.
Gillberg, C. (2010). The ESSENCE in child psychiatry: Early symptomatic syndromes eliciting neurodevelopmental clinical examinations. *Research in Developmental Disabilities*, *31*, 1543–1551. http://dx.doi.org/10.1016/j.ridd.2010.06.002
Goh, C., & Shaw, R. (2007). The current state of palliative care education in Asia-Pacific. In B. Wee, & N. Hughes (Eds.), *Education in palliative care*. New York: Oxford University Press.

Please cite this article in press as: Baeza-Velasco, C., et al. A connective tissue disorder may underlie ESSENCE problems in childhood. *Research in Developmental Disabilities* (2016), http://dx.doi.org/10.1016/j.ridd.2016.10.011

Grahame, R., & Bird, H. (2001). British consultant rheumatologists' perceptions about the hypermobility syndrome: A national survey. *Rheumatology*, *40*, 559–562.
Grahame, R., & Hakim, A. J. (2006). The rheumatological heritable disorders of connective tissue. *Medicine*, *34*, 424–426. http://dx.doi.org/10.1053/j.mpmed.2006.07.011
Grahame, R., & Hakim, A. J. (2013). Arachnodactyly—A key to diagnosing heritable disorders of connective tissue. *Nature Reviews Rheumatology*, *9*, 358–364. http://dx.doi.org/10.1038/nrrheum.2013.24
Grahame, R., Bird, H. A., & Child, A. (2000). The revised (Brighton 1998) criteria for the diagnosis of benign joint hypermobility syndrome (BJHS). *The Journal of Rheumatology*, *27*, 1777–1779.
Grahame, R. (1999). Joint hypermobility and genetic collagen disorders: Are they related? *Archives of Disease in Childhood*, *80*, 188–191.
Grahame, R. (2008). Hypermobility: An important but often neglected area within rheumatology. *Nature Clinical Practice Rheumatology*, *4*, 522–524.
Grahame, R. (2010). What is the joint hypermobility syndrome? In A. J. Hakim, R. Keer, & R. Grahame (Eds.), *Hypermobility, fibromyalgia and chronic pain*. London: Churchill Livingstone Elsevier.
Grahame, R. (2015). *De l'hypermobilité articulaire au syndrome d'Ehlers-Danlos – Approches diagnostiques et thérapeutiques en Grande-Bretagne Lecture*. Créteil (France): Créteil University. Jun 19.
Gratacos, M., Nadal, M., Martin-Santos, R., Pujana, M. A., Gago, J., Peral, B., et al. (2001). A polymorphic genomic duplication on human chromosome 15 is a susceptibility factor for panic and phobic disorders. *Cell*, *106*, 367–379.
Guilleminault, C., Primeau, M., Chiu, H., Yuen, K. M., Leger, D., & Metlaine, A. (2013). Sleep-disordered breathing in Ehlers-Danlos syndrome: A genetic model of OSA. *Chest*, *144*, 1503–1511. http://dx.doi.org/10.1378/chest.13-0174
Hakim, A. J., & Grahame, R. (2003). Joint hypermobility: Best practice & research. *Clinical Rheumatology*, *17*, 989–1004.
Hakim, A. J., & Grahame, R. (2014). Recognising the scale of joint hypermobility burden: Comment on the article by Mulvey et al. *Arthritis Care & Research*, *66*, 496–498. http://dx.doi.org/10.1002/acr22221
Hakim, A. J., Malfait, F., & De Paepe, A. (2010). The heritable disorders of connective tissue: Epidemiology, nosology and clinical features. In A. J. Hakim, R. Keer, & R. Grahame (Eds.), *Hypermobility, fibromyalgia and chronic pain*. London: Churchill Livingstone Elsevier.
Hamonet, C., Gompel, A., Raffray, Y., Zeitoun, J. D., Delarue, M., Vlamynck, E., et al. (2014). Multiple pains in Ehlers-Danlos syndrome. Description and proposal of a therapy protocol. *Douleurs*, *15*, 264–277. http://dx.doi.org/10.1016/j.douler.2014.09.003
Hamonet, C., Ducret, L., Layadi, K., & Baeza-Velasco, C. (2016). Historia y actualidad del Síndrome de Ehlers-Danlos-Tschernogobow. *Cuadernos De Neuropsicología/Panamerican Journal of Neuropsychology*, *10*, 17–31.
Harris, M. J. (1998). ADD/ADHD and hypermobile joints. *Journal of Paediatrics and Child Health*, *34*, 400–401.
Hasija, R. P., Khubchandani, R. P., & Shenoi, S. (2008). Joint hypermobility in Indian children. *Clinical and Experimental Rheumatology*, *26*, 146–150.
Henderson, S. E., Sudgen, D. A., & Barnett, A. L. (2007). *Movement assessment battery for children-2*. London: Harcourt Asses.
Hershenfeld, S. A., Wasim, S., McNivel, V., Parikh, M., Majewski, P., & So, J. (2016). Psychiatric disorders in Ehlers-Danlos syndrome are frequent, diverse and strongly associated with pain. *Rheumatolology International*, *36*, 341–348. http://dx.doi.org/10.1007/s00296-015-3375-1
Hollertz, O. (2003). Connective tissue significance for mental illness. *Svensk Psykiatri*, *3*, 22–23.
Hollertz, O. (2012). Searching for a biological marker common for both ADHD and EDS. *Lakartidningen*, *109*, 41–42.
Hunter, A., Morgan, A. W., & Bird, H. A. (1998). A survey of Ehlers-Danlos syndrome: Hearing, voice, speech and swallowing difficuties. Is there an underlying relationship? *British Journal of Rheumatology*, *3*, 803–804.
Jaffe, M., Tirosh, E., & Cohen, A. (1988). Joint mobility and motor development. *Archives of Disease in Childhood*, *63*, 159–161.
Kirby, A., & Sugden, D. A. (2007). Children with developmental coordination disorders. *Journal of the Royal Society of Medicine*, *100*, 182–186.
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.
Landgrem, M., Kjellman, B., & Gillberg, C. (1998). Attention deficit disorder with developmental coordination disorders. *Archives of Disease in Childhood*, *79*, 207–212.
Leonard, H. C. (2016). The impact of poor motor skills on perceptual, social and cognitive development: The case of developmental coordination disorder. *Frontiers in Psychology*, *7*, 1–4. http://dx.doi.org/10.3389/fpsyg.2016.00311
Lumley, M. A., Jordan, M., Rubenstein, R., Tsipouras, P., & Evans, M. I. (1994). Psychosocial functioning in the Ehlers–Danlos syndrome. *American Journal of Medical Genetics*, *53*, 149–152.
Maillard, S., & Murray, K. J. (2003). Hypermobility syndrome in children. In R. Keer, & R. Grahame (Eds.), *Hypermobility syndrome. Recognition and management for physiotherapist*. London: Butterworth Heinemann.
Mallorqui-Bagué, N., Garfinkel, S. N., Engels, M., Eccles, M., Eccles, J. A., Pailhez, G., et al. (2014). Neuroimaging and psychophysiological investigaction of the link between anxiety, enhanced affective reactivity and interoception in people with joint hypermobility. *Frontiers in Psychology*, *14*, 5–1162. http://dx.doi.org/10.3389/fpsyg.2014.01162
Metlaine, A. (2016). Sommeil et fatigue chez les patients souffrant de syndrome d'Ehlers-Danlos. *Journal De Réadaptation Médicale*, *36*, 62–63. http://dx.doi.org/10.1016/j.jrm.2015.09.009
Mulvey, M. R., Macfarlane, G. J., Beasley, M., Symmons, D. P., Lovell, K., Keeley, P., et al. (2013). Modest association of joint hypermobility with disabling and limiting musculoskeletal pain: Results from a large-scale general population-based survey. *Arthritis Care & Research*, *65*, 1325–1333. http://dx.doi.org/10.1002/acr.21979
Narcisi, A. J., Richards, A. J., Ferguson, S. D., & Pope, F. M. (1994). A family with Ehlers-Danlos syndrome type III/articular hypermobility syndrome has a glycine 637 to serine substitution in type III collagen. *Human Molecular Genetics*, *3*, 1617–1620.
Pacey, V., Tofts, L., Adams, R. D., Munns, C. F., & Nicholson, L. L. (2015). Quality of life prediction in children with joint hypermobility syndrome. *Journal of Paediatrics and Child Health*, *51*, 689–695. http://dx.doi.org/10.1111/jpc.12826
Pailhez, G., & Bulbena, A. (2013). Co-Morbid anxiety and physical disorders: A possible common link with joint hypermobility syndrome. In F. Durbano (Ed.), *New insights into anxiety disorders*. InTech.
Piek, J. P., Bradbury, G. S., Elsley, S. C., & Tate, L. (2008). Motor coordination and social-emotional behavior in preschool-aged children. *International Journal of Development and Education*, *55*, 143–151.
Plenty, S., Heurlin, D., Arlinde, C., & Bejerot, S. (2013). Applying an ESSENCE framework to undertanding adult Autism Spectrum Disorders and ADHD: Retrospective parent reports of childood problems. *Scientific World Journal*, *25*, 469594. http://dx.doi.org/10.1155/2013/469594
Rigoli, D., Piek, J. P., & Kane, R. (2012). Motor coordination and psychosocial correlates in a normative adolescent sample. *Pediatrics*, *129*, e892–e900. http://dx.doi.org/10.1542/peds.2011-1237
Rimmer, J., Giddings, C. E. B., Cavalli, L., & Hartley, B. E. J. (2008). Dysphonia—A rare early symptom of Ehlers-Danlos syndrome? *International Journal of Pediatric Otorhinolaryngology*, *72*, 1889–1892.
Rombault, L., Malfait, F., Cools, A., De Paepe, A., & Calders, P. (2010). Musculoskeletal complaints, physical activity and health-related quality of life among patients with the Ehlers-Danlos syndrome hypermobility type. *Disabililty and Rehabilitation*, *32*, 1339–1345. http://dx.doi.org/10.3109/09638280903514739
Rombault, L., Malfait, F., De Wandele, I., Cools, A., Thijs, Y., De Paepe, A., et al. (2011). Medication, surgery, and physiotherapy among patients with the hypermobility type of Ehlers-Danlos syndrome. *Archives of Physical Medicine and Rehabilitation*, *92*, 1106–1112.
Romeo, D. M., Lucibello, S., Musto, E., Brogna, C., Ferrantini, G., Velli, C., et al. (2016). Assesing joint hypermobility in preschool-aged children. *The Journal of Pediatrics*, http://dx.doi.org/10.1016/j.jpeds.2016.05.072, in press
Russek, L. N., LaShomb, E. A., Ware, A. M., Wesner, S. M., & Westcott, V. (2016). United States physical therapists' knowledge about joint hypermobility syndrome compared with fibromyalgia and rheumatoid arthritis. *Physiotherapy Research International*, *21*, 22–35. http://dx.doi.org/10.1002/pri.1613

Please cite this article in press as: Baeza-Velasco, C., et al. A connective tissue disorder may underlie ESSENCE problems in childhood. *Research in Developmental Disabilities* (2016), http://dx.doi.org/10.1016/j.ridd.2016.10.011

Rustioni, D.M.L. (1994). Prove di valutazione della comprensione linguistica. Firenze (Italy): Giunti O.S. Organizzazioni Speciali.
Sanjay, P., Bagalkoti, P. S., & Kubasadgoudar, R. (2013). Study of correlation between hypermobility and body mass index in children aged 6–12 years. *Indian Journal of Physiotherapy and Occupational Therapy*, *7*, 247–249.
Schalkwijk, J., Zweers, M. C., Steijlen, P. M., Dean, W. B., Taylor, G., van Vlijmen, I. M., et al. (2001). A recessive form of the Ehlers-Danlos syndrome caused by tenascin-X deficiency. *The New England Journal of Medicine*, *345*, 1167–1175.
Scheper, M. C., Engelbert, R. H. H., Rameckers, E. A. A., Verbunt, J., Remvig, L., & Juul-Kristensen, B. (2013). Children with generalized joint hypermobility and musculoskeletal complaints:state of the art on diagnostics, clinical characteristics, and treatment. *BioMed Research International*, http://dx.doi.org/10.1155/2013/121054. ID121054
Schoemaker, M. M., & Kalverboer, A. F. (1994). Social and affective problems of children who are clumsy: How early do they begin? *Adapted Physical Activity Quartely*, *11*, 130–140.
Shetreat-Klein, M., Shinnar, S., & Rapin, I. (2014). Abnormalities of joint mobility and gait in children with Autism Spectrum Disorders. *Brain and Development*, *36*, 91–96. http://dx.doi.org/10.1016/j.braindev.2012.02.005
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, K. G. (1992). Autism and ehlers danlos syndrome. *Journal of the American Academy of Child and Adolescent Psychiatry*, *31*, 173.
Simon, V., Czobor, P., Bálint, S., Mészáros, A., & Bitter, I. (2009). Prevalence and correlates of adult attention-deficit hyperactivity disorder: Meta-analysis. *British Journal of Psychiatry*, *194*, 204–211. http://dx.doi.org/10.1192/bjp.bp.107.048827
Sinibaldi, L., Ursini, G., & Castori, M. (2015). Psychopathological manifestations of joint hypermobility and joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type: The link between connective tissue and psychological distress revised. *American Journal of Medical Genetics*, *169C*(Part C), 97–106. http://dx.doi.org/10.1002/ajmg.c.31430
Smith, T. O., Easton, V., Bacon, H., Jerman, E., Armon, K., Poland, F., et al. (2014). The relationship between bening joint hypermobility syndrome and psychological distress: A systematic review and meta-analyses. *Rheumatology*, *53*, 114–122. http://dx.doi.org/10.1093/rheumatology/ket317
Takei, A., Mera, K., Sato, Y., & Haraoka, Y. (2011). High-functioning autistic disorder with Ehlers-Danlos syndrome. *Psychiatry and Clinical Neurosciences*, *65*, 605–606. http://dx.doi.org/10.1111/j.1440-1819.2011.02262.x
Tantam, D., Evered, C., & Hersov, L. (1990). Asperger's syndrome and ligamentous laxity. *Journal of the American Academy of Child and Adolescent PsychiatryAmerican Academy of Child and Adolescent Psychiatry*, *29*, 892–896.
Tinkle, B. T., Bird, H. A., Grahame, R., Lavallee, M., Levy, H. P., & 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 Medical Genetics Part A*, *149A*, 2368–2370. http://dx.doi.org/10.1002/ajmg.a.33070
Tirosh, E., Jaffe, M., Marmur, M., Taub, Y., & Rosenberg, Z. (1991). Prognosis of motor development and joint hypermobility. *Archives of Disease in Childhood*, *66*, 931–933.
Varni, J., Rapoff, M., Waldron, S., Gragg, R., Bernstein, B., & Lindsey, C. B. (1996). Hronic pain and emotional distress in children and adolescents. *Journal of Developmental and Behavioral Pediatrics*, *17*, 154–161.
Verbraecken, J., Declerck, A., Van den Heyning, P., De Backer, W., & Wouters, E. F. (2001). Evaluation for sleep apnea in patients with Ehlers-Danlos syndrome and Marfan: A questionnaire study. *Clinical Genetics*, *60*, 360–365.
Voermans, N. C., Knoop, H., Bleijenberg, G., & van Engelen, B. G. (2010). Pain in Ehlers-Danlos syndrome is common, severe, and associated with functional impairment. *Journal of Pain and Symptom Management*, *40*, 370–378. http://dx.doi.org/10.1016/j.jpainsymman.2009.12.026
Zweers, M. C., Bristow, J., Steijlen, P. M., Dean, W. B., Hamel, B. C., Otero, M., et al. (2003). Haploinsufficiency of TNXB is associated with hypermobility type of Ehlers-Danlos syndrome. *American Journal of Human Genetics*, *73*, 214–217.

Please cite this article in press as: Baeza-Velasco, C., et al. A connective tissue disorder may underlie ESSENCE problems in childhood. *Research in Developmental Disabilities* (2016), http://dx.doi.org/10.1016/j.ridd.2016.10.011