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REVIEW ARTICLE

Attention-deficit/hyperactivity disorder, joint hypermobility-related disorders and pain: expanding body-mind connections to the developmental age

Carolina Baeza-Velasco[1,2,5] · **Lorenzo Sinibaldi**[3] · **Marco Castori**[4]

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) and generalized joint hypermobility (JH) are two separated conditions, assessed, and managed by different specialists without overlapping interests. Recently, some researchers highlighted an unexpected association between these two clinical entities. This happens in a scenario of increasing awareness on the protean detrimental effects that congenital anomalies of the connective tissue may have on human health and development. To review pertinent literature to identify possible connections between ADHD and GJH, special emphasis was put on musculoskeletal pain and syndromic presentations of GJH, particularly the hypermobile Ehlers–Danlos syndrome. A comprehensive search of scientific databases and references lists was conducted, encompassing publications based on qualitative and quantitative research. Impaired coordination and proprioception, fatigue, chronic pain, and dysautonomia are identified as potential bridges between ADHD and JH. Based on these findings, a map of the pathophysiological and psychopathological pathways connecting both conditions is proposed. Although ADHD and JH are traditionally separated human attributes, their association may testify for the dyadic nature of mind-body connections during critical periods of post-natal development. Such a mixed picture has potentially important consequences in terms of disability and deserves more clinical and research attention.

Keywords Attention-deficit/hyperactivity disorder · Connective tissue · Developmental coordination disorder · Ehlers–Danlos syndrome · Fibromyalgia · Joint hypermobility · Pain

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is an early-onset, neurodevelopmental disorder characterized by persistent symptoms of inattention and/or hyperactivity-impulsivity that get in the way of daily life or typical development. Three subtypes of ADHD are considered: inattentive, hyperactive-impulsive, and combined inattentive and hyperactive-impulsive (American Psychiatric Association 2013) (Table 1). Symptoms of ADHD may persist in adulthood in nearly two-thirds of affected developing children (Faraone et al. 2006). In most of the ethnicities, prevalence of ADHD is around 5% in children and 2.5% in adults (American Psychiatric Association 2013), and it is most frequently diagnosed and treated in males than females (Skogli et al. 2013) with a sex ratio of approx. 3:1 (Gaub and Carlson 1997). Although the etiology of ADHD remains yet unknown, genetic defect and environmental factors are considered having a role in its etio-pathogenesis (Zhou et al. 2015). In particular,

✉ Carolina Baeza-Velasco
carolina.baeza-velasco@parisdescartes.fr

1 Laboratory of Psychopathology and Health Processes, University Paris Descartes - Sorbonne Paris Cité, Boulogne Billancourt, France

2 INSERM U1061 Neuropsychiatry: Epidemiological and Clinical Research, Department of Emergency Psychiatry and Acute Care, CHU Montpellier, Montpellier, France

3 Division of Cytology and Cytogenetics, Belcolle Hospital, Viterbo, Italy

4 Division of Medical Genetics, IRCCS-Casa Sollievo della Sofferenza, San Giovanni Rotondo, Foggia, Italy

5 Institut de Psychologie, Université Paris Descartes, 71 Avenue Edouard Vaillant, 92100 Boulogne-Billancourt Cedex, France

Table 1 DSM-5 diagnostic criteria for ADHD (American Psychiatric Association 2013)

A. A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by (1) and/or (2):

1. *Inattention* six (or more) of the following symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level, and that negatively impacts directly on social and academic/occupational activities. The symptoms are not solely a manifestation of oppositional behavior, defiance, hostility, or failure to understand tasks or instructions. For adolescents and adults (age 17 and older), 5 or more symptoms are required

   Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or with other activities

   Often has trouble holding attention on tasks or play activities

   Often does not seem to listen when spoken to directly

   Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., loses focus and side-tracked)

   Often has trouble organizing tasks and activities

   Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort

   Often loses things necessary for tasks and activities (e.g., school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones)

   Is often easily distracted by extraneous stimuli

   Is often forgetful in daily activities

2. *Hyperactivity and impulsivity* Six (or more) of the following symptoms of hyperactivity-impulsivity for children up to age 16, or five or more for adolescents 17 and older and adults; symptoms of hyperactivity-impulsivity have been present for at least 6 months to an extent that is disruptive and inappropriate for the person's developmental level

   Often fidgets with or taps hands or feet, or squirms in seat

   Often leaves seat in situations when remaining seated is expected

   Often runs about or climbs in situations where it is not appropriate (adolescents or adults may be limited to feeling restless)

   Often unable to play or take part in leisure activities quietly

   Is often "on the go" acting as if "driven by a motor"

   Often talks excessively

   Often blurts out an answer before a question has been completed

   Often has trouble waiting his/her turn

   Often interrupts or intrudes on others (e.g., butts into conversations or games)

In addition, the following conditions must be met

Several inattentive or hyperactive-impulsive symptoms were present before age 12 years

Several symptoms are present in two or more setting, (such as at home, school, or work; with friends or relatives; in other activities)

There is clear evidence that the symptoms interfere with, or reduce the quality of, social, school, or work functioning

The symptoms are not better explained by another mental disorder (such as a mood disorder, anxiety disorder, dissociative disorder, or a personality disorder). The symptoms do not happen only during the course of schizophrenia or another psychotic disorder

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Specify whether:

314.01 (F90.2) Combined presentation If both Criterion A1 (inattention) and Criterion A2 (hyperactivity-impulsivity) are met for the past 6 months

314.00 (F90.0) Predominantly inattentive presentation If Criterion A1 (inattention) is met, but Criterion A2 (hyperactivity-impulsivity) is not met for the past 6 months

314.01 (F90.1) Predominantly hyperactive/impulsive presentation If Criterion A2 (hyperactivity-impulsivity) is met, but Criterion A1 (inattention) is not met over the past 6 months

Specify if:

In partial remission When full criteria were previously met, fewer than the full criteria have been met for the past 6 months, and the symptoms still result in impairment in social, academic, or occupational functioning

Specify current severity:

Mild Few, if any, symptoms in excess of those required to make the diagnosis are present, and symptoms result in only minor functional impairments

Moderate Symptoms or functional impairment between "mild" and "severe" are present

Severe Many symptoms in excess of those required to make the diagnosis, or several symptoms that are particularly severe, are present, or the symptoms result in marked impairment in social or occupational functioning

research indicates that ADHD can be best defined as the quantitative extreme of a spectrum of symptoms continuously distributed in the general population. Literature review suggests that ADHD can be largely explained by the interaction of genetic and non-shared environmental factors with familial clustering, a mechanism compatible with vertical transmission of the risk alleles and non-Mendelian aggregation of the resulting phenotype (Brikell et al. 2015).

Joint hypermobility (JH) defines the ability that a joint has to move beyond normal limits. Rough data indicate a high rate of JH in the general population with predominance in females (6–57% in females vs. 2–35% in males) (Remvig et al. 2007). JH may be localized to a single or few joints, as well as appreciated in multiple body sites (i.e., generalized JH). Although generalized JH is not a medical problem *per se,* it, sometimes, may represent the clue for an underlying systemic disorder. Hereditary connective tissue disorders are the genetic conditions that most commonly present with generalized JH (Castori et al. 2017; Castori and Hakim 2017). Generalized fragility and/or laxity of the various non-ossified connective tissues is the pathologic milieu of hereditary connective tissue disorders. Among them, Ehlers–Danlos syndromes (EDS) are one of the best-known conditions featuring generalized JH.

EDS groups together various constitutional disorders characterized by JH, abnormalities of the skin texture, and fragility and dysfunctions of vessels and internal organs (Callewaert et al. 2008). In 2017, an updated classification of EDS and related disorders has been published under the guidance of the International Consortium on the Ehlers–Danlos Syndromes (Bloom et al. 2017; Malfait et al. 2017). The need of revising the Villefranche nosology was based on the increasing number of phenotypes and genes associated with EDS, and the new concepts risen around JH and its clinical manifestations. Now, 13 different types of EDS are recognized, with the classical, vascular, and hypermobile variants being the most common (Table 2). Among them, hypermobile EDS (hEDS) remains likely the most prevalent, although stricter criteria for its diagnosis are

Table 2 New classification of the Ehlers–Danlos syndromes (Malfait et al. 2017)

Subtype (abbreviation)	Subtype in previous classification	Inheritance	Genes	Major features
Classical EDS (cEDS)	Classic	AD	*COL5A1, COL5A2, COL1A1 (rare)*	Papyraceous and hemosiderotic scars Velvety, hyperextensible skin
Classical-like (clEDS)	Tenascin XB-deficient	AR	*TNXB*	Velvety, hyperextensible skin
Cardiac valvular (cvEDS)	Cardiac valvular	AR	*COL1A2*	Severe cardiac valvular involvement Velvety, hyperextensible skin
Vascular (vEDS)	Vascular	AD	*COL3A1*, *COL1A1* (rare)	Extensive easy bruising Vascular accidents/ruptures
Hypermobile (hEDS)	Hypermobility	AD	Unknown	Musculoskeletal pain Dislocations
Arthrochalasia (aEDS)	Arthrochalasia	AD	*COL1A1*, *COL1A2*	Marked joint hypermobility Bilateral hip dysplasia
Dermatosparaxis (dEDS)	Dermatosparaxis	AR	*ADAMTS2*	Extreme skin fragility Velvety, hyperextensible skin
Kyphoscoliotic (kEDS)	Kyphoscoliotic type 1 Kyphoscoliotic type 2	AR AR	*PLOD1* *FKBP14*	Congenital, progressive scoliosis Congenital hypotonia
Brittle cornea syndrome (BCS)	Brittle cornea syndrome type 1 Brittle cornea syndrome type 2	AR AR	*ZNF469* *PRDM5*	Thin cornea Early-onset keratoconus/globus
Spondylodysplastic (spEDS)	Progeroid type 1 Progeroid type 2 Spondylocheiro-dysplastic	AR AR AR	*B4GALT7* *B3GALT6* *SLC39A13*	Short stature Congenital hypotonia Limb bowing
Musculocontractural (mcEDS)	Musculocontractural type 1 or Kosho type Musculocontractural type 2	AR AR	*CHST14* *DSE*	Velvety, hyperextensible skin Congenital contractures Facial features
Myopathic (mEDS)	Myopathy overlap	AD or AR	*COL12A1*	Congenital hypotonia Proximal contractures
Periodontal (pEDS)	Periodontal	AD	*C1R, C1S*	Severe, early-onset periodontitis Tibial plaques

AD autosomal dominant, *AR* autosomal recessive

established. The former joint hypermobility syndrome (JHS) (Grahame et al. 2000), a clinical diagnosis parallel to the former Ehlers–Danlos syndrome hypermobility type according to the Villefranche nosology (Beighton et al. 1998), has been removed. A continuous spectrum of phenotypes is now recognized, spanning from isolated, non-syndromic JH to hEDS. The gap between the two ends is filled by the newly defined hypermobility spectrum disorders (HSDs). They are exclusion diagnoses and potentially transitory phenotypes used to define all affected individuals not respecting the new hEDS criteria and not presenting a causative mutation in any known disease-gene (Castori and Hakim 2017; Castori et al. 2017). Therefore, the terms hEDS and HSDs substitute all the previously used ones, such as EDS-HT (i.e., EDS hypermobility type), JHS, and benign joint hypermobility syndrome. In particular, the combination hEDS/HSDs is used in this manuscript to indicate the continuous spectrum bridging these categories and to substitute the acronym JHS/EDS-HT, appeared in the past literature.

The association between ADHD and generalized JH is preliminary. Such a novel evidence does not necessarily reflect coincidence, statistical limitations, or a lax pathogenic link. In fact, professionals used to assess JH and those evaluating ADHD rarely observe patients from the same perspective. Anecdotal observations suggest a marked excess of generalized JH in both children and adults with ADHD (Baeza-Velasco et al. 2015b; Harris 1998; Hollertz 2003, 2012). Two preliminary case-control studies confirmed such an impression in ADHD children (Koldas Dogan et al. 2011; Shiari et al. 2013). Complementary, ADHD seems a quite common comorbidity in families with hEDS/HSDs (Castori et al. 2014).

The aim of this review was to identify and trace the possible interconnections between congenital laxity of the connective tissue and impaired development of attention and activity in order to define the rationale for future, more systematic studies.

Methods

This study consisted in a NCBI's PubMed search with the following research string: "['Ehlers–Danlos syndrome' or EDS or hypermobility] AND [attention or hyperactivity or ADHD]." All relevant articles detected in this phase were further scrutinized for additional references not appeared in this search. Recent evidence points out an extension of the EDS-related (and, especially, hEDS/HSDs-related) phenotypic spectrum, which involves practically all major systems and organs (Castori et al. 2013). While hEDS/HSDs have been considered a benign trait, contemporary research indicates this condition as a potentially disabling with pain and fatigue representing the most relevant disability determinants in hEDS/HSDs (Voermans and Knoop 2011). These disabilities (i.e., pain and fatigue) are more prominent and investigated in hEDS/HSDs, but they may be present with a wide range of degree also in other EDS subtypes (Colombi et al. 2015).

Accordingly, the range of potentially overlapping comorbidities between ADHD and EDS may be wider than expected. Literature was further explored on the association of developmental coordination disorder (DCD) and fibromyalgia, both considered commonly, but separately associated with ADHD and EDS (or JH). The terms "developmental coordination disorder," "dyspraxia," and "fibromyalgia" were matched with "Ehlers–Danlos syndrome," "EDS," "hypermobility," "attention deficit," "hyperactivity," and "ADHD".

ADHD, joint hypermobility and Ehlers–Danlos syndromes

The relationship between ADHD and JH was first evoked by Harris (1998), who reported that, in his clinical experience with 200 patients with ADHD, near 99% of them also showed JH. Two recent control-case studies explored generalized JH in children with ADHD. In the first study, the rate of generalized JH was significantly higher in the ADHD group ($n = 54$: generalized JH = 31.5%) compared to controls ($n = 36$; generalized JH = 13.9%) (Koldas Dogan et al. 2011). Comparably, the second study found a higher prevalence of generalized JH among children with ADHD ($n = 86$; generalized JH = 74.4%) than controls ($n = 86$; generalized JH = 12.8%) (Shiari et al. 2013). Recently, Glans et al. (2017), observed, in non-clinical adults, that women with a score > 3/5 at the 5-point questionnaire for JH (Hakim and Grahame 2003) had significantly higher scores in questionnaires assessing hyperactive and impulsive ADHD traits. Concerning the presence of a common link between EDS and ADHD, Hollertz (2003, 2012) alerted about the frequent co-occurrence of EDS and ADHD and stressed the pertinence to search for a genetic marker common to both clinical entities. Recently, it has been observed that 8 out 23 Italian patients with hEDS/HSDs present comorbid ADHD (34.8%) (Castori et al. 2014). Hershenfeld et al. (2016) showed that in a cohort of 106 adults with EDS (JHS from the old nomenclature = 67.9%; cEDS = 16%, unclassified EDS type = 16%, 7% of the whole sample, and 8.3% of patients with hEDS) showed ADHD (Hershenfeld, personal communication). Cederlöf et al. (2016) observed in a nationwide population-based cohort of people with EDS and JHS from the old nomenclature ($n = 1.771$), that individuals with EDS (different subtypes) and their siblings had an increased risk to present ADHD (risk ratio = 5.6; 95%

confidence interval = 4.2–7.4; risk ratio = 2.1; 95% confidence interval = 1.4–3.3, respectively).

Taken together, these papers emphasize phenotypic similarities among a subgroup of patients assessed in a psychiatric and/or developmental setting for suspected neurodevelopmental disorders affecting attention and executive functions, and those referred to the clinical geneticist meant for testing a possible hereditary connective tissue disorder. Even though it seems too premature to assert a full overlap between these two patients' groups, the existence of common pathogenic mechanisms is likely. From this perspective, connective tissue and the increasing number of physiological phenomena, in which it plays a role and that extend much beyond joint mobility and stability, may be crucial for the appropriate development of selected cognitive functions.

ADHD and fibromyalgia

Fibromyalgia is a specific form of widespread musculoskeletal pain syndrome with a strong neuropathic component and features of central pain sensitization (Smith et al. 2011). Fibromyalgia is a quite common comorbidity of ADHD. In fibromyalgia patients from the Netherlands, a high rate of adults with ADHD has been reported (Derksen et al. 2015), and an excess of childhood history of ADHD in women with fibromyalgia has been observed in Spanish patients (Reyero et al. 2011). Many fibromyalgia patients present lack of concentration, which is a core feature of ADHD, and both disorders share a series of unspecific symptoms such as sleep, low energy and unexplained fatigue, poor regulation of body temperature, gastrointestinal problems (reflux, gastritis, and constipation/diarrhea), urinary frequency, widespread musculoskeletal pain, numbness and tingling, heart-related symptoms (i.e., chest tightness, palpitations), allergies, asthma, bronchitis, sinusitis, and poor coordination (Davis and Stephens 2002; Young and Redmond 2007). Moreover, the premorbid lifestyle of patients with fibromyalgia and chronic fatigue syndrome is characterized by a high level of "action-proneness," "overactivity," "ergomania," or "hyperactivity" has been highlighted in different studies (Masquelier et al. 2011; Van Houdenhove et al. 2001; Vlaeyen and Morley 2004). More than 70% of fibromyalgia and chronic fatigue patients describe a high level of involvement in multiple activities with incessant thoughts and ruminations related to these activities, leading to an irresistible urge to move and action described by the patients as "my mind never rest" (Masquelier et al. 2011). Such a clinical pattern play a role as a predisposing, initiating, and maintaining factor of chronic pain, as it has been illustrated by the model "stop rules and current mood" (Vlaeyen and Morley 2004), which may explain the dichotomic relationship of these patients toward their body/mind motion ranging from an excessive activity to a complete abandonment.

The pathogenic link between ADHD and fibromyalgia remains speculative. However, a clue may come from the common finding of dysautonomia in fibromyalgia patients (Martínez-Martínez et al. 2014). The latest diagnostic criteria for fibromyalgia include screening for various somatic symptoms, many of them with a likely dysautonomic origin (Wolfe et al. 2016). Recently, a significant role of autonomic failure toward cognitive symptoms was emphasized in a range of neurologic and neuropsychiatric disorders. It has been proposed that a documented fall in blood pressure fulfilling the criteria for orthostatic hypotension and/or autonomic-reflex impairment can affect cognitive performances (Bassi and Bozzali 2015). Memory deficits have been also associated with autonomic dysregulation in healthy populations (Saint Martin et al. 2013). A poorer global cognitive function was demonstrated in elders with orthostatic hypotension (Frewen et al. 2014), while selective attention and cognitive processing are impaired in adults with postural orthostatic tachycardia syndrome (Arnold et al. 2015; Raj, Haman, Raj et al. 2009). More specifically, in 61 preschooler children, poorer orthostatic pulse pressure regulation in response to an orthostatic challenge resulted associated with an increased risk for symptoms of ADHD (Casavant et al. 2012). Therefore, it is possible that fibromyalgia and ADHD share an underlying dysautonomia (either symptomatic or asymptomatic for additional cardiovascular complaints). The historically different time frame of disease diagnosis between fibromyalgia (a diagnosis typical of adulthood) and ADHD (a diagnosis typical of the developmental age) may also explain as to why medical literature is only recently putting in evidence such an association.

Joint hypermobility, Ehlers–Danlos syndromes, and fibromyalgia

By the end of the last century, much more attention was posed on generalized JH as a predisposing factor to widespread chronic musculoskeletal pain. The old Brighton criteria for JHS clearly define such a non-casual association by identifying generalized JH (with a Beighton score ≥ 4) and arthralgia in 4 or more joints as major diagnostic criteria (Grahame et al. 2000). The association between generalized JH and fibromyalgia was identified in child and adult populations. Gedalia et al. (1993) reported that 17 out of 21 children with fibromyalgia (81%) also showed generalized JH. In addition, Ting et al. (2012) reported that 58 out of 122 (48%) children with juvenile fibromyalgia were noted to have hypermobile joints by their primary rheumatologist. Although some authors rose perplexities concerning such an association (Ting et al. 2012), the finding was

also confirmed in adults (Ofluoglu et al. 2006; Sendur et al. 2007). In this regard, generalized JH was described in 18 out of 66 (27.3%) women with fibromyalgia (Ofluoglu et al. 2006). Subsequently, a more recent study observed that 51 out of 75 (68%) fulfilled Brighton criteria for JHS (Kozanoglu et al. 2016). Clark et al. (2014) meanwhile reported that among hEDS/HSDs patients ($n = 90$), 19% had also FM, and Murray et al. (Murray et al. 2013) reported 42% of FM in adults with hEDS/HSDs. Comparably to fibromyalgia, an instrumental clue for central sensitization of pain was found in hEDS/HSDs patients (Di Stefano et al. 2016).

Rowe et al. (1999) obtained the first evidence for a tight link between EDS and autonomic dysfunction in 11 children (6 with EDS classical type and 6 with hEDS/HSDs), all showing either postural orthostatic tachycardia or neurally mediated hypotension. Gazit et al. (2003) found orthostatic hypotension, postural orthostatic tachycardia, and uncategorized orthostatic intolerance in 21 out of 27 (78%) hEDS/HSDs patients. De Wandele et al. (2014a, b) pointed out the role of dysautonomia in the pathogenesis of various features of EDS. These authors found that the autonomic burden in EDS, and more particularly in hEDS/HSDs, is comparable to that in fibromyalgia. The same research group further investigated the dysautonomic profile of hEDS/HSDs with autonomic functional testing. They found a higher low-frequency/high-frequency ratio (i.e., an increase of the physiological heart rate variability), a greater blood pressure falls during Valsalva maneuver and a smaller initial systolic blood pressure increase during tilt in a cohort of 39 affected women compared to controls. They also found postural orthostatic tachycardia as the most prevalent autonomic profile in hEDS/HSDs and identified sympathetic neurogenic dysfunction as the most likely explanation for dysautonomia in this condition (De Wandele et al. 2014b). Similar results were obtained in an independent study on 35 Italian adults with hEDS/HSDs (Celletti et al. 2017).

Taken together, these data suggest that both fibromyalgia and cardiovascular dysautonomia are common in EDS and, more specifically, hEDS/HSDs and that their comorbidity represents a major source of disability in the complex patient. It is therefore plausible that an underlying dysautonomia may represent the biological phenomenon bridging the gap between a preexisting generalized JH and the resulting fibromyalgia. More specifically, a faulty in autonomic regulation may facilitate the transition from asymptomatic GJH through chronic symptoms. hEDS/HSDs seems a prototype of such a phenomenon.

ADHD and developmental coordination disorder

ADHD frequently co-occurs with motor problems. Indeed, even though this feature is not generally considered in ADHD assessment, not being included in the diagnostic criteria for the diagnosis, it is increasingly apparent that it is part of the clinical picture characterizing ADHD individuals. In fact, children with ADHD may show difficulties with motor coordination and control, repetitive and sequential movements, balance and motor excessive overflow, defined as unintentional and unnecessary movements accompanying voluntary activity (Macneil et al. 2011; Mostofsky et al. 2003). These features have been described to be correlated to motor cortex inhibition (Gilbert et al. 2001). A recently published comprehensive review of the studies about ADHD children motor skills confirmed that most cases showed motor problems and highlighted the importance to assess these features stressing the relationship between sensorimotor and cognitive skills (Kaiser et al. 2014). Noteworthy, several studies in ADHD children showed that about 50% of them also meet the criteria of DCD (Cairney et al. 2010; Gillberg and Kadesjö 2003; Piek et al. 1999), a neurodevelopmental disorder in which motor impairments are a core characteristic (American Psychiatric Association 2013). Such a relationship might be underlying by executive functions, suggesting brain deficit in those affected (Rosa Neto et al. 2015). Cerebellar abnormalities may also play a role in the balance problems and in the difficulties in maintaining an erect posture using proximal muscles of the column, which have been observed in ADHD children (Rosa Neto et al. 2015; Stray et al. 2009).

Despite the high co-occurrence of ADHD and DCD, probably sharing etiopathogenic neurodevelopmental issues (Dyck et al. 2011; Gillberg 2010; Stray et al. 2009), there is poor awareness about the relationship between motor problems and psychiatric conditions among mental health professionals. This can be partially explained by the fact that the patient's families often show big difficulties in dealing with hyperactivity and impulsivity. Thus, these disruptive behaviors rather than motor difficulties motivate specialist seeking. The treatment of these problematic behaviors is one of the priorities in the activities of the developmental disability services (Green et al. 2005). Additionally, ADHD is mainly addressed to the child psychiatrist while motor problems and DCD are rather evaluated and treated by neurologists and pediatricians (Gillberg and Kadesjö 2003). Such a split in the diagnostic process makes the holistic approach, which would be the optimum, very difficult to achieve often leaving motor problems to the background with an underdiagnosed/undertreated status (Hill et al. 2016).

Joint hypermobility, Ehlers–Danlos syndromes, and developmental coordination disorder

Children and adults with generalized JH and patients with EDS (mostly hEDS/HSDs) often present peculiar motor and coordination attributes. The non-casual association between (simple) motor delay and generalized JH was first noted in the '1970s–1990s of the last century in three studies on healthy children or toddlers with motor delay, which showed that generalized JH specifies for a benign form of selective motor retardation distinct from other progressive disorders (e.g., muscle dystrophies) (Benady and Ivanans 1978; Jaffe et al. 1988; Tirosh et al. 1991). GJH is a common finding in DCD patients (Celletti et al. 2015; Jelsma et al. 2013; Morrison et al. 2013), and the full spectrum of hEDS/HSDs is likely a commonly underreported comorbidity in DCD children (Kirby et al. 2005; Kirby and Davies 2007). Complementarily, children with generalized JH have a poorer motor competence and balance compared to non-hypermobile children, and this more often occurs in males and younger individuals (Easton et al. 2014; Falkerslev et al. 2013; Schubert-Hjalmarsson et al. 2012). Clumsiness, developmental dyspraxia and DCD, voice, and speech difficulties are quite common in hEDS/HSDs children and adults (Adib et al. 2005; Castori et al. 2014; Hunter et al. 1998).

As recently emphasized (Ghibellini et al. 2015), impaired proprioception might be the background dysfunction contributing to defective coordination skills in generalized JH and hEDS/HSDs. Accordingly, various research groups showed reduced proprioceptive performance of the knees in adults and children with these conditions (Fatoye et al. 2009; Hall et al. 1995; Mallik et al. 1994; Pacey et al. 2014; Rombaut et al. 2011; Sahin et al. 2008). While Rombaut et al. (2011) failed to replicate this observation at the shoulders, Mallik et al. (1994) found impaired position sense also at the proximal interphalangeal joints of fingers. Poor position sense at the hands can affect fine motor skills and handwriting and could result in poor manipulation competences and dysgraphia in the developing child. On the other hand, poor proprioception at the knee joints may trigger a different pattern of muscle activation of the lower limbs (Greenwood et al. 2011) and significantly affect balance and lateral trunk stability (Falkerslev et al. 2013; Rombaut et al. 2011; Pacey et al. 2014). Balance is also affected at rest under the challenge of the vestibular system, and this may be explained by vestibular deficiency and/or insufficient proprioceptive capabilities of the neck (Iatridou et al. 2014). Interestingly, Rigoldi et al. (2013) suggest that motor and cognitive competences may be further hampered by the need of concentrating more attention on maintaining posture due to poor balance control. All these data indicate that proprioception is affected by JH in both the non-syndromic and syndromic patient and that, this phenomenon, in turn, can affect balance, coordination, and concentration skills.

Discussion

Recent literature identifies in ADHD and generalized JH a likely non-casual association. As these two conditions affect two traditionally separated attributes of the human being, such an association may testify for the dyadic nature of the mind-body connections during critical periods of post-natal development. Similarly, this already occurred for anxiety disorders and generalized JH, whose significant association was acutely registered for the first time in 1988 by Bulbena and collaborators (1988) and, subsequently, scrutinized by the same and other research groups (Bulbena et al. 2017; Baeza-Velasco et al. 2015a, 2017; Sinibaldi et al. 2015). In particular, strong evidence supports the direct association between anxiety, simple phobia, social phobia, panic, agoraphobia, and severity of anxiety with the presence of generalized JH, assessed by the Beighton score and/or the 5-point questionnaire (Sinibaldi et al. 2015). While most studies on anxiety and GJH were focused on adults, the combination of ADHD and GJH is more typical of the pediatric age, when brain development is much more sensitive to external stimuli which, in turn, may more easily leave long-lasting effects on emotions, cognition, and behavior. Although contemporary evidence on the concurrence of ADHD and generalized JH is still preliminary, these two conditions share a series of comorbidities, which reinforce statistical evidence and offer deeper insights on the underlying pathogenesis and psychopathology, particularly, both ADHD and JH often concur with fibromyalgia and DCD. Interpretation of the pertinent literature is a hard task, and this is mainly related to the non-overlapping nature of the medical fields involved in these diagnoses. While ADHD and DCD are managed by child neurologists and developmental psychologists, fibromyalgia is often diagnosed by rheumatologists and adult neurologists. In an attempt of deciphering the reasons as to why ADHD seems to cluster with generalized JH, at least four different, but not mutually exclusive pathways could be identified:

1. Generalized JH and hEDS/HSDs are commonly characterized by impaired proprioception which likely affects balance, posture, and coordination; in this scenario, maintaining motor competences may generate a request overload to executive functions and attention, which, in turn, generate ADHD.
2. Musculoskeletal pain (e.g., fibromyalgia in adults and growing pain in children), so commonly associated with

generalized JH and hEDS/HSDs, may directly affect attention and concentration skills, as well as other cognitive functions, in both adults and children.

3. Fibromyalgia and hEDS/HSDs often combine with dysautonomia, which was recently linked to cognitive, and attention troubles both in health and disease. Noteworthy, the association between memory and cognitive issues, dysautonomia, generalized JH, and hEDS/HSDs has been recently suggested (Bravo 2012; Eccles et al. 2014).
4. ADHD and generalized JH (and hEDS/HSDs) are pleiotropic manifestations of the same preexisting (genetic) cause, which simultaneously affects the development and functions of periarticular connective tissue and brain.

Each of them is reasonable and deserves attention from an experimental and clinical point of view in order to improve our knowledge on the complexities of the body-mind connections and to offer immediate tools to better classify, prognosticate, and hopefully, treat patients (Fig. 1). Caution should be applied in the interpretation of chronic musculoskeletal pain, such as fibromyalgia, in the etiopathogenesis and manifestations of ADHD in children. In fact, while growing pain is a common form of recurrent, often non-neuropathic form of pain in the pediatric patient, true fibromyalgia is rarer in children.

Preliminary evidence suggests the existence of a link between brain structure and JH in the generation/expression of specific psychiatric comorbidities, in particular, anxiety disorders. In particular, in 72 non-clinical subjects, JH (measured with the Beighton score) correlates positively with the volume of the left lateral occipital cortex and negatively with the right superior temporal cortex and bilateral inferior parietal cortices (Eccles et al. 2012). Subsequently, the same group examined 36 healthy volunteers with interoceptive sensitivity tests, JH (Beighton score), and questionnaires for anxiety and body awareness tendency. The study demonstrates that interoceptive sensitivity can mediate the positive association between state anxiety score and extent of JH (Mallorquí-Bagué et al. 2014). Accordingly, it has been postulated that specific brain regions have a role in connecting psychological processes and the physiological state of the body in the generation of anxiety in individuals with JH (Eccles et al. 2014, 2015). The same might hold true also for the association between ADHD and JH and EDS. Interestingly, some brain regions, such as anterior cingulate and parietal lobe, which show a decreased volume in non-clinical JH volunteers, are implicated in attention, while others (e.g., inferior parietal cortex) can affect proprioceptive awareness (Eccles et al. 2012).

The potential association between ADHD and generalized JH prompts us to approach the issue from a wider perspective. For example, in hEDS/HSDs, its multisystemic manifestations, also comprising the neurodevelopmental features, lead to an accumulation of several sectorial diagnoses by the same individual at different ages (Ghibellini et al. 2015). This often generates confusion in the mind of patients and their relatives, who feel very unlucky due to the great number of "chance" concurrences of different diseases. In this regard, the Nordic concepts of DAMP (i.e., Deficit in Attention, Motor Control and Perception; Gillberg et al. 1982) and ESSENCE (i.e., Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations; Gillberg 2010) are particularly relevant in the hEDS/HSDs context (Baeza-Velasco et al. 2017). These clinical and conceptual entities diverge from ADHD discrete diagnostic approach overlooking other highly frequent concomitant problems such as motor difficulties. DAMP consider motor problems as a feature of a broader syndrome, in which impaired attention deficit (with or without impaired hyperactivity/impulsivity) concurs with impaired deficit in gross or fine motor, perception or speech-language in the absence of overt intellectual disability or cerebral palsy (Gillberg and Kadesjö 2003). Thus, basically DAMP corresponds to ADHD combined to DCD, which is the clinical reality observed in about half

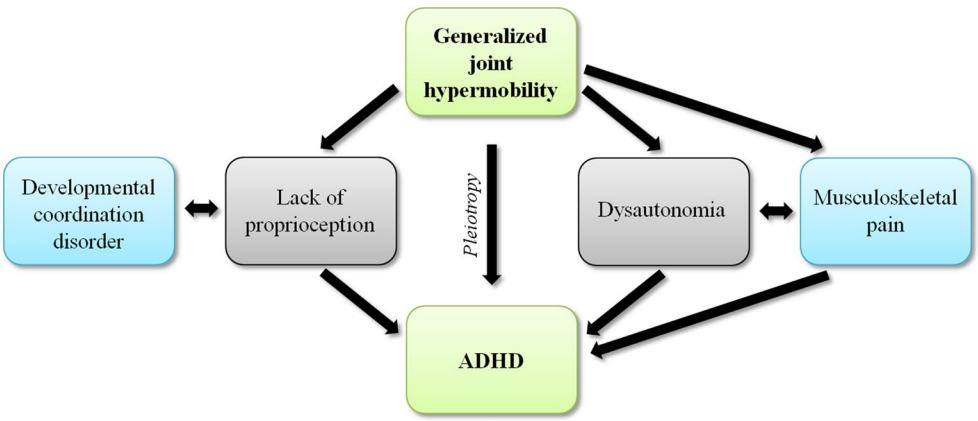

Fig. 1 A schematic summary of the possible pathophysiological connections between generalized joint hypermobility, Ehlers–Danlos syndrome, and attention-deficit/hyperactivity disorder

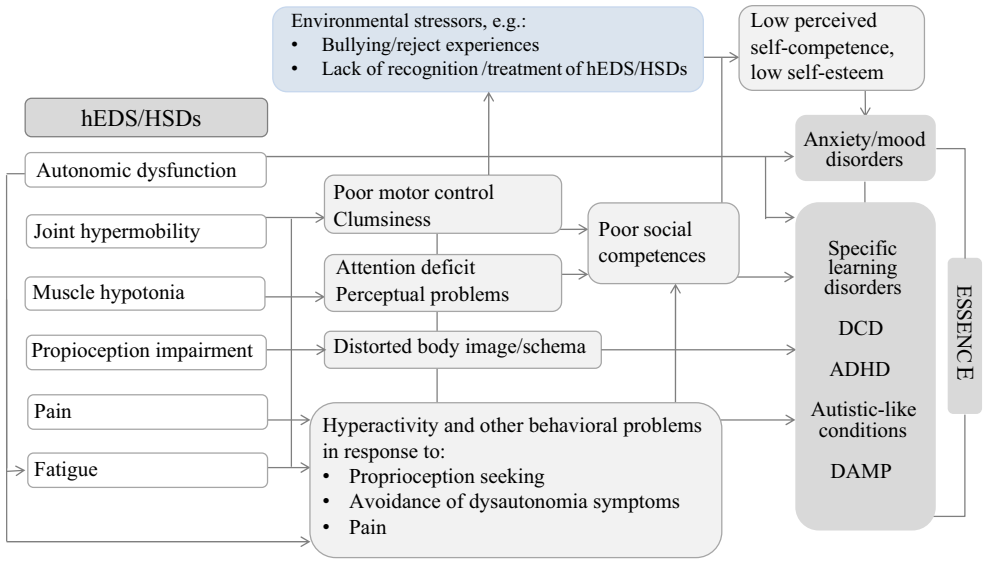

Fig. 2 Diagram illustrating possible relationships between some features of JHS/EDS-HT might contributing to neurodevelopmental disorders and psychopathology in the developmental age. JHS/EDS-HT: joint hypermobility syndrome/Ehlers–Danlos syndrome hypermobility type. *ADHD* attention-deficit/hyperactivity disorder, *DCD* developmental coordination disorder, *DAMP* deficits in attention, motor control, and perceptual abilities, *ESSENCE* early symptomatic syndromes eliciting neurodevelopmental clinical examinations

of ADHD cases (Ferlini and Neri 2016). Similarly, the ESSENCE approach highlights the need to explore clusters of neurodevelopmental problems in the first 5 years of life. These problems include the general development, communication and language, social interrelatedness, motor coordination, attention, activity, behavior, mood, sleep, and feeding domains. The co-occurrence of them is often the rule rather than the exception (Gillberg 2010). Thence, DAMP and ESSENCE draw attention to different coexisting domains to identify children with multiple needs (Cairney et al. 2010; Gillberg and Kadesjö 2003; Gillberg 2010) and are consistent with the neurodevelopmental picture observed in hEDS/HSDs patients and generalized JH individuals. Thus, DAMP and ESSENCE approaches seem clinically useful and suitable to a more holistic taking charge of this condition (Baeza-Velasco et al. 2017).

More recently, Bulbena et al. (2015) introduced the concept of "neuroconnective phenotype" consisting in the description of the psychosomatic mechanisms involved around the well-established association between generalized JH and anxiety. This model was intended to fill up the current nosologic gap concerning clinical situations in which there is a combination of somatic and psychopathological aspects. hEDS/HSDs is a good example of such mixed clinical situations, as many patients present a wide range of psychological and psychiatric burdens in addition to the overt musculoskeletal, mucocutaneous, and visceral dysfunctions (Murray et al. 2013). In the neuroconnective phenotype, features of people presenting generalized JH and anxiety are organized in five dimensions: somatic symptoms, somatosensory symptoms, somatic illnesses, psychopathology, and the behavioral dimension, which includes patterns of increased and decreased activity. In this regards, and as a possible extension of this model, the body-mind connections in younger populations with generalized JH and hEDS/HSDs should be also elucidated. As above mentioned, ADHD is likely a common finding in hypermobile individuals in developmental age, but such a relationship is probably just an edge of a wider picture comprising other neurodevelopmental problems. Figure 2 illustrates some possible connections between generalized JH and hEDS/HSDs, on the one end, and their neurodevelopmental outcomes/attributes, on the other end. Generalized JH may affect brain plasticity during development due to its changing consequences on muscle tone, posture, and movement.

Figure 1 summarizes a possible pathogenic pathway linking generalized JH to ADHD via the concurrence of lack of proprioception (clinically manifesting with DCD), dysautonomia, and musculoskeletal pain. If these links exist, they should act independently from the background phenotype featuring generalized JH. Nevertheless, data are still too scanty to assume such a phenomenon. In other words, while available information suggests us to consider ADHD a "consequence" or a clinical manifestation of generalized JH, we cannot exclude that ADHD and generalized JH occur in the same individual as primary features of a systemic disorder caused by mutations in a pleiotropic gene. Only studies in patients with well-defined syndromes caused by mutations in distinct genes may help in understanding whether the association between generalized JH and ADHD is a marker of

specific genotype–phenotype correlations, or rather a common comorbidity shared by different disorders.

Conclusions

The emerging complex connections between ADHD, DCD, generalized JH, and the prototypic hEDS/HSDs recapitulate the unsaid needs that modern medicine has of breathing a more holistic approach especially in order to understand and manage chronic disabilities. In the "hypermobile" patient, a more generalized defect of the non-ossified connective tissue may influence neuroplasticity by a plethora of mechanisms due to the possible simultaneous detrimental effects on nervous system and various visceral functions. Patients' subphenotyping and longitudinal studies are needed to identify the trajectories of children with ADHD and other (only apparently isolated) neurodevelopmental disorders and to find more tailored prevention and treatment programs for these patients.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to disclose.

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