ORIGINAL RESEARCH

Prevalence of ADHD and Autism Spectrum Disorder in Children with Hypermobility Spectrum Disorders or Hypermobile Ehlers-Danlos Syndrome: A Retrospective Study

Erik Kindgren [1,2]
Antonia Quiñones Perez[1]
Rajna Knez [1,3]

[1]Department of Pediatrics, Skaraborg Hospital, Skövde, Sweden; [2]Division of Pediatrics, Department of Biomedical and Clinical Sciences (BKV), Medical Faculty, Linköping University, Linköping, Sweden; [3]Sahlgrenska Academy, Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden

Introduction: Hypermobility spectrum disorders (HSD) and hypermobile Ehlers-Danlos syndrome (hEDS) are both characterized by generalized hypermobility, in combination with pain, affected proprioception, and pronounced fatigue. Clinical observation indicates that behavioral problems, hyperactivity, and autistic traits are overrepresented in children with those conditions. The purpose of this retrospective study was to establish the prevalence of attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) among children with HSD and hEDS treated in our clinic since 2012.

Subjects and Methods: Since Ehlers-Danlos syndrome (EDS) diagnostic criteria and international classification were changed in 2017, we equate the older diagnosis EDS hypermobility type with the newer hEDS and the older hypermobility syndrome with HSD. A registry search from the computerized medical record system found 201 children (88 boys, 113 girls) aged 6–18 years who were treated at our pediatrics department with the diagnoses HSD or EDS. All medical records (113 with HSD, 88 with EDS) were reviewed, and key symptoms such as fatigue and pain, as well as diagnosis of ADHD/ASD, were recorded.

Results: All EDS cases could be classified as hEDS. Of the entire study cohort, 16% had a verified ADHD diagnosis and a further 7% were undergoing ADHD diagnostic investigation. Significantly more children with hEDS had ADHD compared to children with HSD (p=0.02). In the age group 15–16 years, 35% of those with hEDS had ADHD and, among those aged 17–18 years, ADHD was present in 46%. Children with coexisting ADHD showed a significantly higher proportion of associated symptoms such as fatigue, sleep-problems, and urinary tract problems. ASD had been verified in 6% of the children. Of those with ASD, 92% had sleep problems.

Conclusion: This study shows a strong association between HSD or hEDS and ADHD or ASD. Therefore, children with HSD or hEDS may need to be routinely screened for neuropsychiatric symptoms.

Keywords: ADHD, autism spectrum disorder, children, hypermobility spectrum disorder, Ehlers-Danlos syndrome

Correspondence: Erik Kindgren
Department of Pediatrics, Skaraborg Hospital, Lövängsvägen, Skövde, 541 42, Sweden
Tel +46104739222
Fax +46500478356
Email erik@kindgren.org

Introduction

There are 13 different diseases known as Ehlers-Danlos Syndrome (EDS), which usually creates misunderstanding for both patients and healthcare professionals.

Twelve of the diseases in the EDS group have verified genetics and are very rare, such as classical EDS (prevalence: 5 per 100,000) and vascular EDS (prevalence: 2–3 per 1,000,000).[1] For hypermobile EDS (hEDS), a genetic cause has not yet been verified, and this disease is much more common than other EDS subtypes. The prevalence of hEDS may be at least 10 per 100,000[1] but the reported figure varies in different studies. Several recent data sources indicate a prevalence from 0.75–2%, and even up to 3.4% in the study to provide a quantification, using joint hypermobility and widespread pain as a proxy for hEDS.[2]

Hypermobility is a clinical sign that shows that the range of motion in one or more joints is greater than is considered normal. If the diagnostic criteria for hEDS are not fulfilled but hypermobility is present, the condition may often be classified as a hypermobile spectrum disorder (HSD).[1] HSD and hEDS are both characterized by generalized hypermobility in combination with pain, impaired proprioception, and pronounced fatigue.[2]

There is insufficient knowledge of the underlying mechanisms of pain and fatigue experienced by children with HSD or hEDS. Effective treatments are lacking for this patient group, and a recent meta-analysis has shown that most interventions lack efficacy to improve the functioning of these children.[3,4] They also risk developing chronic pain and suffering exclusion in society.[5,6] Children with HSD or hEDS show lower self-reported health-related quality of life compared to healthy children, which has been found to be associated with their pain and fatigue.[7] A recently published retrospective study has shown that patients with EDS and those with HSD share a common psychiatric presentation.[8]

In everyday clinical practice, we have observed several patient cases with difficult-to-treat pain or pain syndrome (both with and without hypermobility) in whom the pain problems have almost completely regressed since the patient received a diagnosis of attention-deficit/hyperactivity disorder (ADHD) and received treatment with central nervous system (CNS) stimulant drugs, such as methylphenidate. Clinically, there is also a clear overrepresentation of behavioral problems and hyperactivity, as well as autistics traits, in children with HSD or hEDS. This has aroused our interest to explore in more detail the relationship between HSD or hEDS on the one hand and ADHD or autism spectrum disorder (ASD) on the other.

There are several studies suggesting that hEDS and HSD may be associated with ADHD, though ADHD appears to be more common with HSD than with EDS.[8] There is also increasing evidence that ASD is more common in individuals with joint hypermobility-related disorders than expected by chance.[9] A Swedish national registry study has recently shown that there is a positive association between EDS and ASD or ADHD, and similar results have been observed for HSD.[10]

Both ADHD and ASD are neurodevelopmental disorders,[9,11] which accounts for their similarities as well as for the differences among them. A recent study by Berenguer et al showed that children with ASD (ASD alone or in co-occurrence with ADHD) showed worse theory of mind skills than children with ADHD, while children with ADHD symptomatology (ADHD alone or with co-occurring ASD) had a more extensive profile of executive functions (EF) deficits than children with ASD only.[12] Findings obtained by Craig et al, in their systematic review of EF deficit in ASD and ADHD, are in line with the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, where these two neurodevelopmental disorders are no longer mutually exclusive. Authors have concluded, based on neurocognitive endophenotype, that rather than a separate condition with distinct impairments, it seems that the common co-occurence of EF deficit reflects an additive comorbidity.[13]

The etiology of ADHD is not yet completely understood[11,14] and most cases of ASD are of unknown cause.[9] Thus, it is not surprising that accepted theories about the underlying mechanisms for relationships between hEDS or HSD and these neurodevelopmental disorders are lacking. Baeza-Velasco et al recently published an explanatory model with at least four different but not mutually exclusive pathways, showing the possible relationships between ADHD and hypermobility: (1) impaired proprioception and, consequently, situations where maintaining motor competences may overload executive functions and attention; (2) musculoskeletal pain that may directly affect attention and concentration; (3) a link between dysautonomia (which is overrepresented in HSD and hEDS) and cognitive difficulties; and (4) ADHD and hypermobility having different expressions with a common genetic background.[11]

Based on these issues and our clinical experience, in this medical records study we wanted to explore our hypothesis that children with HSD or hEDS have a greater risk of developing ADHD and ASD than the normal population. The Ehlers-Danlos diagnostic criteria were changed in 2017 but we presume that the results of

our retrospective study can be relevant to future clinical work because, for example, one study found a similar frequency of comorbidities of hEDS (such as gastrointestinal dysfunction and psychological comorbidities) in those patients who met the new criteria and those who did not.[15]

Materials and Methods

A registry search from the computerized medical record system covering the period from 2012 to 2018 found 201 children aged 6–18 years who were treated at the pediatric and youth medicine clinic at Skaraborg Hospital, Sweden, with the diagnoses Q79.6 Ehlers-Danlos syndrome or M35.7 Hypermobility syndrome (ICD-10).[16]

A review of all 201 medical records (113 with hypermobility syndrome and 88 with EDS) was conducted, and the following variables were recorded: gender, age, place of residence, diagnosis, age at diagnosis, Beighton hypermobility score, fatigue, pain, sleep problems, snoring, sleep apnea, continuous positive airway pressure (CPAP) treatment, abdominal pain, constipation, diarrhea, reflux, gastritis, nausea, nutritional problems in childhood, urinary tract problems, ADHD, age at ADHD diagnosis, pharmacological treatment for ADHD, suspected ADHD, autism, Asperger's syndrome, fulfilment of the old Villefranche criteria for EDS hypermobility type (EDS-ht) from 1997,[17] and fulfilment of the new criteria for hEDS from 2017.[18,19] Because our registry data predated this change in 2017, we have used the older EDS-ht as a proxy for the newer diagnosis hEDS, as described by the International Consortium on the Ehlers-Danlos Syndromes.[2] We also equate the older hypermobility syndrome with its replacement HSD, in accordance with the 2017 nomenclature changes. Concerning neuropsychiatric symptoms, we equate the registered diagnoses of autism and Asperger's syndrome with the umbrella diagnosis ASD, in accordance with the nomenclature change in 2013 in the DSM-5.[20] The children in our study were subdivided in two groups based on the diagnosis from the medical records. Thus, in the first group (HSD group) we have 113 children with M35.7 Hypermobility syndrome while in the other group (hEDS group) we have children with Q79.6 Ehlers-Danlos syndrome. None of the children had been diagnosed with, or exhibited symptoms of, any of the rare forms of EDS, such as vascular EDS. Four children were re-examined for classical EDS or classical-like EDS but did not meet the diagnostic criteria. This allowed us to classify all the 88 EDS cases as hEDS, since we equate EDS-ht with hEDS.

The choice of targeting key symptoms (fatigue, pain, sleep problems, gastrointestinal symptoms, urinary tract problems, and neuropsychiatric symptoms) was based on clinical experience with the patient group in the study.

The total number of children in each age group in Skaraborg was obtained through Statistics Sweden, SCB, and in total there were 38,901 children in the age group 6–18 years.[21] The proportion of children with an ADHD diagnosis in Skaraborg was obtained through a register search from the computerized records system.

The Beighton hypermobility scale is a nine-point scale with scores for the presence of any of the following: (a) palmar flexion of the wrist and flexion of the thumb to the volar side of the forearm (one point for each hand), (b) passive dorsal flexion of the little finger more than 90° (one point for each hand), (c) hyperextension of the elbow more than 10° (one point for each arm), (d) hyperextension of the knee joints more than 10° (one point for each leg), and (e) back flexion with legs straight and palms on the floor.[19]

Statistical Analysis

The normal distribution for independent variables was analyzed both graphically and with the Shapiro–Wilk test and then Levene's test for equal variance. The chi-squared test was used to compare categorical variables (gender and symptoms) between the diagnostic groups. t-tests were used to compare continuous variables (age and scores on the Beighton hypermobility scale) between gender and diagnostic groups. The statistics were calculated using SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

Ethical Considerations

The study was performed in accordance with the Declaration of Helsinki and was approved by the Regional Ethical Review Board of Western Sweden (approval number 998–18). Due to the retrospective design and lack of study-related interventions, written informed consent was waived. All patient data accessed for the purposes of this investigation complied with relevant data protection and privacy regulations.

Results

A diagnosis of EDS was noted in 88 of 201 children and a diagnosis of hypermobility syndrome (here classified as HSD) in 113 of 201 (see Table 1). All of the EDS cases could be classified as hEDS because none of these children

Table 1 Study Population: Age, Gender, and Distribution of Associated Symptoms in Each Diagnosis Group

	All	HSD	hEDS	p-value
	n=201	**n=113**	**n=88**	
Gender				
Boys, n (%)	88 (44%)	47 (42%)	41 (47%)	0.479
Girls, n (%)	113 (56%)	66 (58%)	47 (53%)	
Age, years				
All, mean (SD)	12.0 (3.5)	12.0 (3.5)	12.1 (3.7)	0.871
Boys, mean (SD)	11.5 (3.4)	11.3 (3.7)	11.8 (3.1)	0.491
Girls, mean (SD)	12.5 (3.6)	12.5 (3.2)	12.4 (4.1)	0.807
Boys vs girls	p = 0.059	p = 0.056	p = 0.453	
Age at diagnosis, years				
All, mean (SD)	7.88 (3.79)	8.27 (3.68)	7.84 (3.97)	0.095
Boys, mean (SD)	6.82 (2.92)	6.79 (2.80)	6.85 (3.08)	0.916
Girls, mean (SD)	8.71 (4.19)	9.33 (3.88)	7.83 (4.47)	0.059
Boys vs girls	**p < 0.001**	**p < 0.001**	p = 0.162	
Pain, n (%)	156 (78%)	85 (76%)	71 (81%)	0.417
Fatigue, n (%)	114 (57%)	52 (46%)	62 (71%)	**0.001**
Sleep-related symptoms				
Sleep problems, n (%)	91 (45%)	45 (40%)	46 (52%)	0.079
Snoring, n (%)	6 (3%)	3 (3%)	3 (3%)	0.755
Sleep apnea, n (%)	9 (5%)	3 (3%)	6 (7%)	0.157
CPAP treatment, n (%)	2 (1%)	0 (0%)	2 (2%)	0.107
Gastrointestinal symptoms				
Presence of at least one symptom, n (%)	119 (52%)	61 (54%)	58 (66%)	0.088
Abdominal pain, n (%)	52 (26%)	28 (25%)	24 (27%)	0.689
Constipation, n (%)	85 (42%)	43 (38%)	42 (48%)	0.168
Reflux/gastritis, n (%)	35 (17%)	17 (15%)	18 (21%)	0.316
Diarrhea, n (%)	6 (3%)	4 (4%)	2 (2%)	0.600
Nutrition problems during childhood, n (%)	5 (3%)	1 (1%)	4 (5%)	0.098
Urinary tract problems, n (%)	27 (13%)	11 (10%)	16 (18%)	
Neuropsychiatric symptoms				
ADHD verified/diagnosed, n (%)	32 (16%)	12 (11%)	20 (23%)	**0.020**
ADHD under investigation/suspected, n (%)	14 (7%)	11 (10%)	3 (3%)	0.081
ASD, n (%)	13 (6%)	5 (4%)	7 (8%)	0.295
Beighton hypermobility score				
All, mean (SD)	4.92 (1.96)	4.67 (1.85)	5.23 (2.06)	0.052
Boys, mean (SD)	4.79 (2.02)	4.42 (1.84)	5.21 (2.15)	0.079
Girls, mean (SD)	5.01 (1.91)	4.84 (1.85)	5.25 (1.99)	0.279
Boys vs girls	p = 0.451	p = 0.245	p = 0.922	

Notes: *t*-tests were used for comparisons of continuous variables and chi-squared tests for categorical variables; Bold text indicates a statistically significant difference with a p-value less than 0.05.
Abbreviations: HSD, hypermobility spectrum disorders; hEDS, hypermobile Ehlers-Danlos syndrome; ASD, autism spectrum disorders, includes Asperger's syndrome.

had been diagnosed with, or exhibited symptoms of, any of the rare forms of EDS.

The gender distribution in the whole group was 44% boys and 56% girls. The hEDS group had a relatively even gender distribution of 47% boys and 53% girls, but in the HSD group there was a slightly skewed distribution: 42% boys and 58% girls. The mean age at diagnosis was 7.9 years. In the hEDS group, boys received their diagnosis just over two years earlier than girls (p < 0.001), and boys in the HSD group received the

diagnosis just over one year earlier than the girls (p < 0.001).

Pain and Fatigue

Pain was noted in 78% of all children, but without significant differences between diagnosis groups. Fatigue was noted in 71% of children in the hEDS group and 46% of those in the HSD group, a statistically significant difference (p = 0.001) (Table 1).

Sleep-Related Symptoms

In the entire study cohort, 45% had some sleep-related symptoms in the form of sleep problems, snoring, or verified sleep apnea. There were no significant differences between diagnosis groups (Table 1).

Gastrointestinal Symptoms

In the entire study cohort, 52% had some form of gastro-intestinal symptoms: abdominal pain, constipation, reflux, gastritis, diarrhea, or nutritional problems. There were no significant differences between diagnosis groups (Table 1).

Neuropsychiatric Symptoms

A verified ADHD diagnosis was found in 16% of the children, while another 7% were under ADHD assessment or suspected ADHD was mentioned in their records. An ADHD diagnosis was significantly more common in the hEDS group, where 23% had a verified diagnosis, than in the HSD group, where 11% had ADHD diagnosis (p = 0.020). In the age group 15–16 years, 35% (13 of 37) of those with hEDS or HSD had an ADHD diagnosis, and in the age group 17–18 years it was 46% (11 of 24). The mean age at which patients in the hEDS group received their ADHD diagnosis was 9.2 years, while in the HSD group this was 9.9 years.

From the total sample, 152 of 201 children were resident in our catchment area. A verified ADHD diagnosis was found in 20% (30 of 152) of those children, while another 7% (11 of 152) were under ADHD assessment, or suspected ADHD was mentioned in their records. This is a significantly higher proportion than in the normal population (usually about 5%),[11] and significantly higher (p < 0.001) compared to all children aged 6–18 years in our catchment area (Skaraborg), where during the period 2015–2018, 5.8% had an ADHD diagnosis. In the age group 17–18, 47% of the children with hEDS or HSD in our catchment area had an ADHD diagnosis.

In the entire cohort, 6.5% (13 of 201), and in our catchment area 7.2% (11 of 152), had a verified diagnosis of autism or Asperger's syndrome in their medical records (reclassified here as ASD). This was a significantly higher proportion (p < 0.001) compared to all children aged 6–18 years in our catchment area, where 2.6% have been diagnosed with ASD.

Associated Symptoms in Children with Neurodevelopmental Disorders

Children with a verified ADHD diagnosis generally showed a higher proportion of associated symptoms compared to children who did not have an ADHD diagnosis (see Figure 1). In the entire study cohort, fatigue (p < 0.001), sleep problems (p < 0.001), and urinary tract problems (p < 0.05) were significantly higher in those with a verified ADHD diagnosis. No significant difference in the proportion with pain or other gastrointestinal symptoms was detected, but a tendency towards a higher incidence of reflux/gastritis was detected in those with an ADHD diagnosis than those without (p = 0.054) (Figure 1). In addition, sleep problems were overrepresented in the group of 14 children undergoing ADHD assessment (71% vs 36%, p = 0.001). In the HSD group, significantly more fatigue (p < 0.001), sleep problems (p < 0.001), and reflux/gastritis (p = 0.036) were found in those with an ADHD diagnosis. In the hEDS group, significantly more sleep problems (p = 0.047) and urinary tract problems (p = 0.020) were found in those with an ADHD diagnosis.

Of those children with an ADHD diagnosis, 56% (18 of 32) had ongoing treatment with CNS stimulants. Comparing the children with ADHD who had this treatment and those who did not, no significant differences were detected for the symptoms sleep problems and pain, but there was a tendency toward fewer sleep problems in the treated group.

Of the children with ASD, 92% had sleep disorders, and this was significantly higher than in those without ASD (p < 0.001) (Figure 2). There were also significant differences in fatigue where the presence was higher among children with coexisting ASD than in those without it (p < 0.05).

Beighton Hypermobility Score

There were no significant gender differences in Beighton scores, but the higher scores in the hEDS group than the HSD group approached statistical significance (p = 0.052) (Table 1).
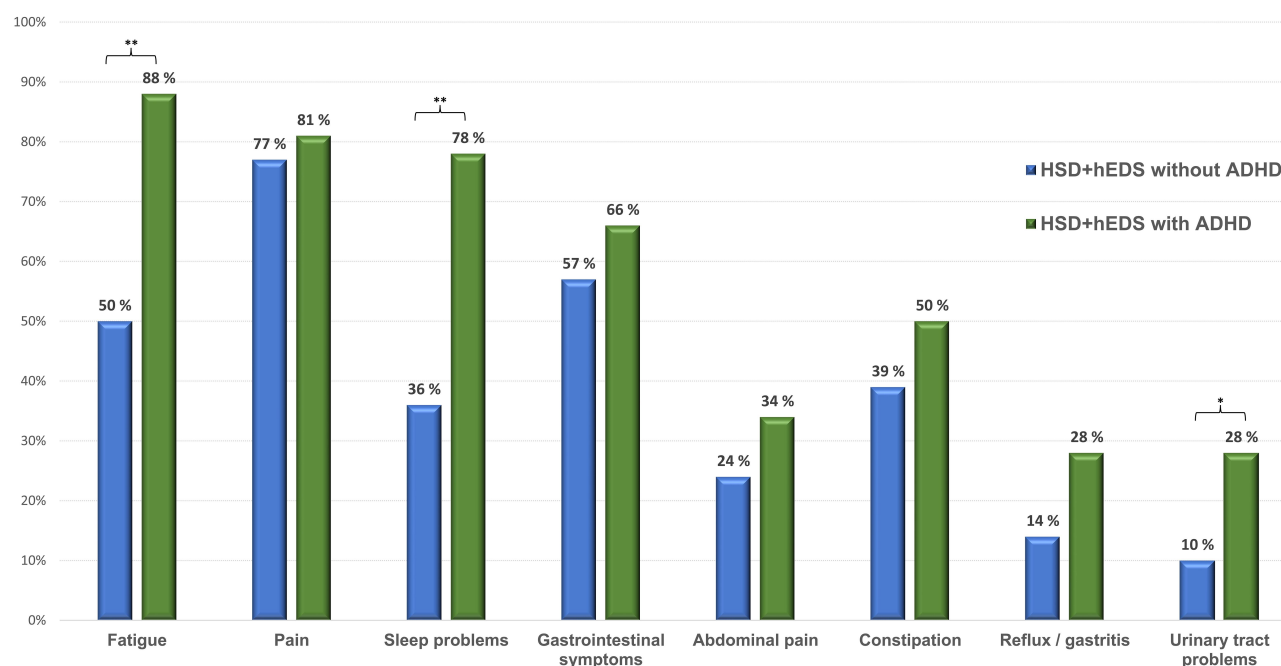
Figure 1 Percentage of associated symptoms in 201 children with HSD or hEDS, comparing those with and without a diagnosis of ADHD. Analyzed with chi-squared tests. *p<0.05; **p<0.001.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; HSD, hypermobility spectrum disorders; hEDS, hypermobile Ehlers-Danlos syndrome.
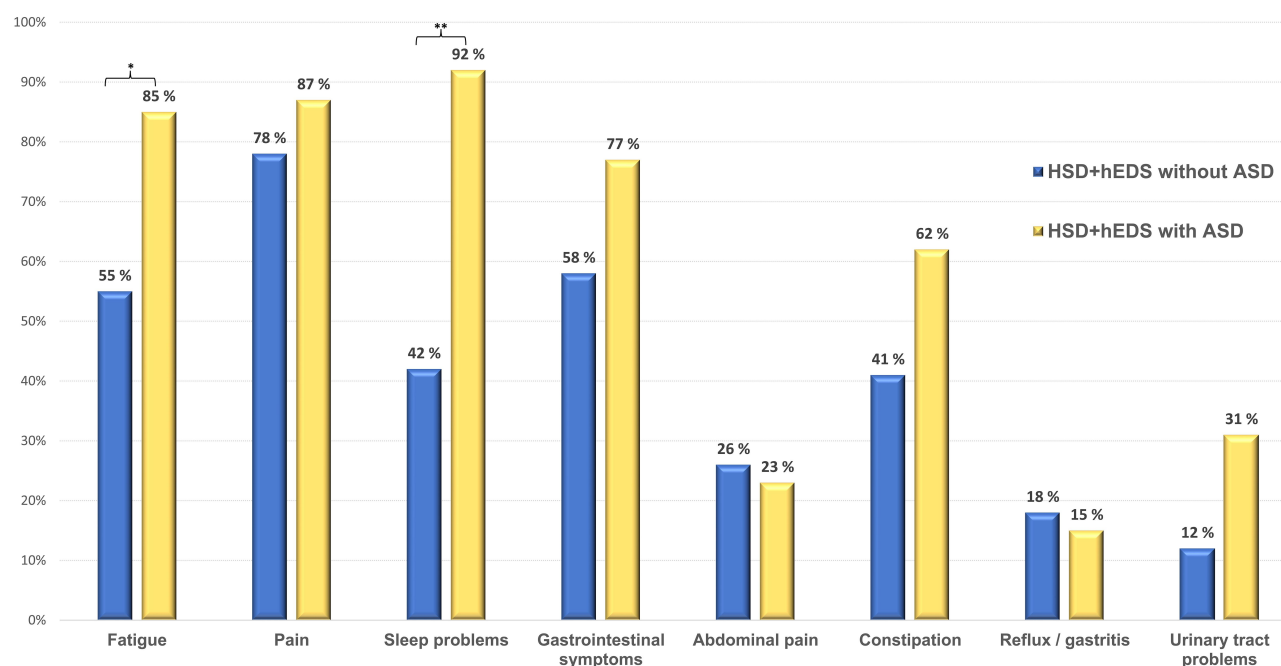

Figure 2 Percentage of associated symptoms in 201 children with HSD or hEDS, comparing those with and without a diagnosis of ASD. Analyzed with chi-squared tests. *p<0.05; **p<0.001.
Abbreviations: ASD, autism spectrum disorders; HSD, hypermobility spectrum disorders; hEDS, hypermobile Ehlers-Danlos syndrome.

For both the hEDS and HSD group, the scores on the Beighton scale were generally slightly higher, but not significantly so, for children with associated symptoms (fatigue, pain, sleep problems, snoring, sleep apnea, CPAP treatment, gastrointestinal symptoms, urinary tract problems, ADHD, and suspected ADHD). Those with ASD had significantly higher Beighton scores (6.22 vs 4.80 points, p = 0.035).

Discussion

The purpose of this register study was to examine whether the clinically observed association between HSD or hEDS and neuropsychiatric symptoms can also be statistically confirmed. The results show that 16% of children with HSD or hEDS also have a verified ADHD diagnosis, which is more than three times higher than the expected rate (about 5%).[11] The rate of ASD among children with HSD or hEDS was also higher, approximately twice the expected rate. The children with neuropsychiatric symptoms or diagnose also had a higher proportion of associated symptoms, in particular fatigue, sleep disorders, and urinary tract problems. However, they did not have more pain.

Boys with HSD or hEDS were diagnosed on average two years earlier than girls, which is well in line with our clinical experience, where we often see boys having the most symptoms before puberty. The problems in the musculoskeletal system then decrease during puberty, probably due to increased muscle mass. A large proportion of the girls do not seek medical care until puberty, when the symptoms and consequent problems seem to increase. The mean age at first HSD/hEDS diagnosis for all our study population is 7.88 years (SD 3.79), with 6.82 (SD 2.92) for boys and 8.71 (SD 4.19) for girls. Results for the boys in our sample are in line with the recently published cohort study where the age at first joint hypermobility syndrome (JHS)/EDS diagnosis peaked in the age group 5–9 years for a male. In contrary, data from our sample show that girls, although diagnosed significantly later than boys, get diagnosis even sooner than in this cohort study where age at first diagnosis peaked in the age group 15–19 years for a female.[22]

In our study, the proportion of children with an ADHD diagnosis was significantly higher in the older age groups, with a verified ADHD diagnosis in almost half of those aged 17–18 (compared to 15% of all children aged 17–18 in our catchment area). Several studies have reported high prevalence of generalized joint hypermobility in patients with attention deficit disorder (ADD) or ADHD,[23] while only a few studies investigate the presence of ADHD in patient with EDS-ht and JHS or hypermobility syndrome. Thus, Castori et al have found that ADHD was present in 34.8% (8 out of the 23) of the patient with JHS/EDS-ht.[24] Although this was a higher prevalence than in our study, it is important to underline that the majority of the whole study population (n=82) in that previous study were adults, and we have noticed that prevalence of ADHD in our

sample is higher in the older age groups. Using the Swedish Patient Register, Cederlöf et al analyzed the association between psychiatric disorders and hypermobility syndrome or EDS (all ages and all 13 subtypes, since they have the same diagnostic code).[10] They found that 4.3% of all EDS patients had an ADHD diagnosis, compared to 0.8% in the control group. Siblings of those with EDS also had an increased incidence of ADHD compared to siblings in the control group. In those persons with hypermobility syndrome, 3.0% had ADHD compared to 0.5% in the control group. EDS was associated with ASD (in 2.9% patients vs. 0.4% in comparison individuals), while 1.6% of patients with hypermobility syndrome had ASD compared to 1.2% controls.[10] Our study population is not completely comparable to the Cederlöf study population, as their study did not separate the EDS types; moreover, they did not separate age groups. However, our results are in line with Cederlöf regarding the higher presence of ADHD among patients with EDS than those with HSD. We have found that significantly more children with hEDS have been diagnosed with ADHD than children with HSD. In contrast to recently published results of the study, in which ADHD was more common in patients with HSD (although an older sample than ours: mean age 36.1) than in those with EDS.[8]

More than half of the children with HSD or hEDS had at least one symptom from the gastrointestinal tract; the most common was constipation, which was reported in over two fifths of the cohort. Children with HSD and coexisting ADHD had significantly higher rates of gastritis and reflux, which is in line with previous studies showing an association between ADHD and gastroesophageal reflux disease.[25] In our study, more than one in eight children with HSD or hEDS had urinary incontinence, of whom those with ADHD had a significantly higher risk of urinary tract problems. The fact that ADHD is more common in children with overactive bladder than in healthy children is already established.[26] The incidence of pain was similar in those with an ADHD diagnosis compared to those without an ADHD diagnosis. Our theory that children with ADHD have an increased sensitivity to pain stimuli was not borne out in our study, nor did treatment with central stimulants result in a reduced frequency of reported pain in the patients' medical records. Since pain perception is associated with ADHD and methylphenidate administration,[27] one would expect differences among groups in our study. However, this was not observed.

Nearly half of the children in our cohort reported sleep problems. The central symptom of fatigue in HSD and hEDS may be associated with sleep problems and coexisting neurodevelopmental disorders. It is known that children with ADHD or ASD are at increased risk of sleep problems.[28–30] Our findings confirm that both fatigue and sleep problems are over-represented in children with a diagnosis of ADHD or ASD. Treatment with CNS stimulants may have an effect on sleep in children with ADHD, but the individual variation in drug response and sleep problems is not completely understood.[31] The tendency toward fewer sleep problems among the children in our cohort who were being treated for ADHD with CNS stimulants, although not statistically significant, warrants further investigation. Interestingly, we saw that sleep problems were strongly over-represented in the group of children who were undergoing investigation for ADHD. This may imply that it is the ADHD symptoms themselves and not the treatment with CNS stimulants that may affect sleep. Children with ASD are at increased risk of sleep disturbances[30] and this was confirmed in our study, where more than 9 in 10 children with ASD had sleep problems.

The degree of hypermobility (according to the Beighton scale) showed no relation to the degree of associated symptoms, which suggests that hypermobility is only a sub-symptom; this has recently been confirmed by McGillis et al.[15] Most of the key observed symptoms were somewhat more common in the hEDS group than the HSD group, although only fatigue and a diagnosis of ADHD were significantly more common; this is what we expected because these are criteria-based diagnoses, and more criteria are required for a hEDS diagnosis than for HSD. However, none of these associated symptoms are included in the hEDS or HSD criteria.[19]

The strength of our study is the use of data from subjects in a naturalistic, clinical setting with a large clinical sample. Our study points to the importance of actively and systematically asking children and their caregivers about associated symptoms of joint hypermobility-related disorders. Pain from the musculoskeletal system often arises as a topic naturally during the clinic visit, but gastrointestinal symptoms, urinary tract problems and, above all, problems related to sleep and neuropsychiatric symptoms should be actively elicited in the patient history. Our results are dependent on what questions the doctor posed at the time of the examination and whether the answer was recorded. We can thus expect our figures to be somewhat low, compared to systematically asking each patient about all these associated symptoms. In addition, it was not possible

to estimate the degree of pain and fatigue through the medical records, as well as the burden of sleep problems. In order to standardize comprehensives of the physician's visit, the authors of the present study have proposed the standardized manual which is now being applied in clinics at every visit of children with suspected HSD/hEDS.

The results obtained in our study derived from a clinical sample at the Department of Pediatrics. In case of suspicion of a neurodevelopmental disorder, children were referred to the Department of Child and Adolescent Psychiatry that, consequently, if they confirmed suspicions as well, performed a diagnostic process according to their own standard diagnostic procedure. However, exploration of the exact diagnostic procedure and diagnostic criteria of neurodevelopmental disorders, that were used, were not part of this study's scope, which is one of the study's limitations. Nevertheless, since the study is retrospective and none of the authors were actively involved in the diagnostic process of neurodevelopmental disorders in our cohort, the possibility for influencing the obtained results is unlikely. In clinical practice we have noticed that children with hEDS/HSD have prominent co-occurring symptoms of ADHD and ASD, and thus, in reviewing medical records, we have focused only on these two neurodevelopmental disorders. Since we have not collected data for all disorders in comorbidity, such as neurological, psychiatric or other neurodevelopmental disorders, this is also a clear limitation to our study. Another weakness of the study is that we have a low number of patients with ASD, which causes statistical difficulties.

Conclusions

In summary, this study showed an unexpectedly large association between neuropsychiatric symptoms and HSD or hEDS. The frequency of sleep disorders was also unexpectedly high. The results of this study indicate that children with these diagnoses may need to be screened for neuropsychiatric symptoms and preferably also for sleep disorders. There is a great need for further research in this area because, from a clinical point of view, it will help to assure the best possible treatment options according to the etiology. Thus, identifying one biological marker for both ADHD and EDS[32] may be one possible direction.

Our research group has recently started a prospective study (the BALTHazar study from Swedish „Barn med symtom på ADHD, Ledsmärta och Trötthet vid Hypermobilitet„ or children with symptoms of ADHD, joint pain, fatigue and hypermobility), with targeted investigations for, among other things, ADHD symptoms, ASD,

and sleep disorders. If these are found to be a major part of the symptomatology in children with HSD and hEDS, then treatment should be focused on these problems, for example through sleep regulation and ADHD treatment.

Author Contributions

All authors made a substantial contribution to the work, whether to its conception and design, acquisition of data, or analysis and interpretation; participation in the drafting or critical reviewing of the article; agreeing about the journal to which the article was submitted; giving final approval of the version to be published; and agreeing to be accountable for all aspects of the work.

Funding

Disclosure

The authors declare no potential conflicts of interest for this work.

References

1. Ehlers-Danlos Syndrom. Socialstyrelsen (the Swedish National Board of Health and Welfare). Available from: https://www.socialstyrelsen.se/ovanligadiagnoser/ehlers-danlossyndrom#anchor_2. Accessed April, 2019.
2. Tinkle B, Castori M, Berglund B, et al. Hypermobile Ehlers-Danlos syndrome (a.k.a. Ehlers-Danlos syndrome type III and Ehlers-Danlos syndrome hypermobility type): clinical description and natural history. *Am J Med Genet C Semin Med Genet*. 2017;175(1):48–69. doi:10.1002/ajmg.c.31538
3. Scheper MC, Juul-Kristensen B, Rombaut L, Rameckers EA, Verbunt J, Engelbert RH. Disability in adolescents and adults diagnosed with hypermobility-related disorders: a meta-analysis. *Arch Phys Med Rehabil*. 2016;97(12):2174–2187. doi:10.1016/j.apmr.2016.02.015
4. Engelbert RH, Juul-Kristensen B, Pacey V, et al. The evidence-based rationale for physical therapy treatment of children, adolescents, and adults diagnosed with joint hypermobility syndrome/hypermobile Ehlers Danlos syndrome. *Am J Med Genet C Semin Med Genet*. 2017;175(1):158–167. doi:10.1002/ajmg.c.31545
5. Ronge E. [EDS and the hypermobility syndrome. Common cause of reduced work capacity]. *Lakartidningen*. 2011;108(45):2318.
6. Smith TO, Easton V, Bacon H, et al. The relationship between benign joint hypermobility syndrome and psychological distress: a systematic review and meta-analysis. *Rheumatology (Oxford)*. 2014;53(1):114–122. doi:10.1093/rheumatology/ket317
7. Pacey V, Tofts L, Adams RD, Munns CF, Nicholson LL. Quality of life prediction in children with joint hypermobility syndrome. *J Paediatr Child Health*. 2015;51(7):689–695. doi:10.1111/jpc.12826
8. Wasim S, Suddaby JS, Parikh M, et al. Pain and gastrointestinal dysfunction are significant associations with psychiatric disorders in patients with Ehlers–Danlos syndrome and hypermobility spectrum disorders: a retrospective study. *Rheumatol Int*. 2019;39(7):1241–1248. doi:10.1007/s00296-019-04293-w
9. Baeza-Velasco C, Cohen D, Hamonet C, et al. Autism, joint hypermobility-related disorders and pain. *Front Psychiatry*. 2018;9:656.
10. Cederlof M, Larsson H, Lichtenstein P, Almqvist C, Serlachius E, Ludvigsson JF. Nationwide population-based cohort study of psychiatric disorders in individuals with Ehlers-Danlos syndrome or hypermobility syndrome and their siblings. *BMC Psychiatry*. 2016;16:207. doi:10.1186/s12888-016-0922-6
11. Baeza-Velasco C, Sinibaldi L, Castori M. Attention-deficit/hyperactivity disorder, joint hypermobility-related disorders and pain: expanding body-mind connections to the developmental age. *Atten Defic Hyperact Disord*. 2018;10(3):163–175. doi:10.1007/s12402-018-0252-2
12. Berenguer C, Roselló B, Colomer C, Baixauli I, Miranda A. Children with autism and attention deficit hyperactivity disorder. Relationships between symptoms and executive function, theory of mind, and behavioral problems. *Res Dev Disabil*. 2018;83:260–269. doi:10.1016/j.ridd.2018.10.001
13. Craig F, Margari F, Legrottaglie AR, Palumbi R, de Giambattista C, Margari L. A review of executive function deficits in autism spectrum disorder and attention-deficit/hyperactivity disorder. *Neuropsychiatr Dis Treat*. 2016;12:1191–1202. doi:10.2147/NDT.S104620
14. Sciberras E, Mulraney M, Silva D, Coghill D. Prenatal risk factors and the etiology of ADHD—Review of existing evidence. *Curr Psychiatry Rep*. 2017;19(1):1. doi:10.1007/s11920-017-0753-2
15. McGillis L, Mittal N, Santa Mina D, et al. Utilization of the 2017 diagnostic criteria for hEDS by the Toronto GoodHope Ehlers–Danlos syndrome clinic: a retrospective review. *Am J Med Genet A*. 2020;182(3):484–492. doi:10.1002/ajmg.a.61459
16. World Health Organization. *ICD-10: International Statistical Classification of Diseases and Related Health Problems: Tenth Revision*. 2nd ed. World Health Organization; 2004.
17. Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). *Am J Med Genet*. 1998;77(1):31–37. doi:10.1002/(SICI)1096-8628(19980428)77:1<31::AID-AJMG8>3.0.CO;2-O
18. Castori M, Tinkle B, Levy H, Grahame R, Malfait F, Hakim A. A framework for the classification of joint hypermobility and related conditions. *Am J Med Genet C Semin Med Genet*. 2017;175(1):148–157. doi:10.1002/ajmg.c.31539
19. Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet*. 2017;175(1):8–26. doi:10.1002/ajmg.c.31552
20. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
21. Statistics Sweden. Available from: https://www.scb.se/en/finding-statistics/statistics-by-subject-area/population/population-composition/population-statistics/. Accessed April, 2019.
22. Demmler JC, Atkinson MD, Reinhold EJ, Choy E, Lyons RA, Brophy ST. Diagnosed prevalence of Ehlers-Danlos syndrome and hypermobility spectrum disorder in Wales, UK: a national electronic cohort study and case-control comparison. *BMJ Open*. 2019;9(11):e031365. doi:10.1136/bmjopen-2019-031365
23. Sinibaldi L, Ursini G, Castori M. Psychopathological manifestations of joint hypermobility and joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type: the link between connective tissue and psychological distress revised. *Am J Med Genet C Semin Med Genet*. 2015;169C(1):97–106. doi:10.1002/ajmg.c.31430
24. Castori M, Dordoni C, Valiante M, et al. 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. *Am J Med Genet A*. 2014;164(12):3010–3020. doi:10.1002/ajmg.a.36805

25. Effatpanah M, Motamed F, Najafi M, et al. Prevalence of attention deficit hyperactivity disorder in pediatrics patients newly diagnosed with gastroesophageal reflux disease. *Int J Pediatr.* 2017;5 (9):5609–5616.

26. Yousefichaijan P, Sharafkhah M, Rafiei M, Salehi B. Attention-deficit /hyperactivity disorder in children with overactive bladder; a case-control study. *J Ren Inj Prev.* 2016;5(4):193. doi:10.15171/ jrip.2016.41

27. Wolff N, Rubia K, Knopf H, et al. Reduced pain perception in children and adolescents with ADHD is normalized by methylphenidate. *Child Adolesc Psychiatry Ment Health.* 2016;10:24. doi:10.1186/s13034-016-0112-9

28. Miano S, Ferri R. Epidemiology and management of insomnia in children with autistic spectrum disorders. *Paediatr Drugs.* 2010;12 (2):75–84. doi:10.2165/11316140-000000000-00000

29. Eyuboglu M, Eyuboglu D. Behavioural sleep problems in previously untreated children with attention deficit hyperactivity disorder. *Psychiat Clin Psych.* 2018;28(1):19–24.

30. Mazzone L, Postorino V, Siracusano M, Riccioni A, Curatolo P. The relationship between sleep problems, neurobiological alterations, core symptoms of autism spectrum disorder, and psychiatric comorbidities. *J Clin Med.* 2018;7(5):102. doi:10.3390/jcm7050102

31. Stein MA, Weiss M, Hlavaty L. ADHD treatments, sleep, and sleep problems: complex associations. *Neurotherapeutics.* 2012;9 (3):509–517. doi:10.1007/s13311-012-0130-0

32. Hollertz O. [Searching for a biological marker common for both ADHD and EDS]. *Lakartidningen.* 2012;109(1–2):41–42.