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Pain and sleep quality in children with non-vascular Ehlers–Danlos syndromes

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Abstract

The objective of this study was to explore the factors contributing to quality of life in pediatric patients with non-vascular Ehlers–Danlos syndromes (EDS). Data were analyzed on 41 children with a diagnosis of non-vascular EDS from the de-identified data available from the National Institute on Aging (NIA) study of heritable disorders of connective tissue. Children under age 19 years were seen as part of a long-term evaluation project from 2003 to 2013 on a larger natural history of patients with heritable disorders of connective tissue. Data collected included medical history, physical examination findings, diagnostic study results, and responses on validated questionnaires. We reviewed a sub-cohort of children with a diagnosis of non-vascular EDS and explored pain severity and interference via the Brief Pain Inventory, and sleep quality via the Pittsburgh Sleep Quality Index. Pain severity had a strong correlation with pain interference, and both were similar to other disorders that include chronic pain reported in the literature. Sleep quality did not correlate with pain severity or interference, but all patients had poor sleep quality in comparison to historical controls. We conclude that pain and sleep are significant issues in the pediatric non-vascular EDS population, and future research may be directed toward these issues.

Keywords

brief pain inventory; Ehlers–Danlos syndrome; hypermobility syndrome; pain; Pittsburgh sleep quality index; sleep quality

1 | INTRODUCTION

The Ehlers–Danlos syndromes (EDS) comprise a heterogeneous group of conditions of connective tissue with a broad spectrum of involvement including the musculoskeletal, cardiac, dermatologic, ophthalmologic, gastrointestinal, autonomic, and neurodevelopmental systems (Malfait et al., 2017). While joint hypermobility is common in the pediatric

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population (10–15% prevalence) (Cattalani et al., 2015), the prevalence of most forms of EDS meeting diagnostic criteria in children ranges from 4.6 to 13% (Tobias et al., 2013; Sperotto et al., 2015), with the hypermobile type being most common. It has been suggested that joint hypermobility syndrome and hypermobility EDS represent a spectrum of the same disorder (Tinkle et al. 2009). There are many types of EDS, the most common being hypermobile and classical (henceforth referred to as non-vascular). Children with non-vascular EDS and/or generalized joint hypermobility with multiple complications are increasingly referred to pediatric genetic clinics for diagnosis and are often hospitalized with exacerbations of chronic illness. Much debate and research are ongoing regarding: (a) the diagnostic criteria for and classification of these conditions, especially in younger children who have been shown to have a wider range of joint mobility variation; (b) the underlying genetic etiology and mechanism of disease of hypermobility EDS; and (c) optimal strategies for addressing patients' complex health needs with a family-centered goal of enhanced well-being.

There has been limited research regarding factors affecting health-related quality of life and management in the pediatric population with Ehlers–Danlos syndromes. Perception of quality of life was assessed in 29 children with hypermobility syndrome compared to healthy controls (Fatoye et al., 2012) using the Peds QL and pain intensity evaluation on a knee joint. The quality of life was worse as compared to healthy children, and there was a negative correlation between pain intensity and perceived quality of life. Pacey et al. (2015) assessed quality of life in 89 Australian children with joint hypermobility syndrome/hypermobility EDS using the Peds QL and measures of fatigue and pain. They found that both the parent and child reported quality of life was worse than for healthy children, and similar to those with cancer, obesity and significant heart disease, and that pain reduction through physical therapy improved parent reported quality of life. A more recent study (Scheper et al., 2017a) assessed functional impairments in 101 children with joint hypermobility syndrome/hypermobility EDS longitudinally and found increasing pain, decreasing endurance and increasing fatigue over time, contribution to disability, and consistently lower quality of life.

In order to assess quality of life in a pediatric sub-cohort of a larger study of disorders of connective tissue, we analyzed a number of factors including pain and sleep. We evaluated the relationship between severity of pain, how much pain interferes with daily activities, and sleep quality. While adult studies have addressed the interaction of pain and sleep in patients with non-vascular types of EDS (Voermans et al., 2010b; Castori et al., 2013), the pediatric age group is not as well studied. Our goal was to evaluate the data available on the pediatric subgroup of a large study population of patients with non-vascular EDS in order to expand the literature, lay the groundwork for future studies and improve clinical care.

2 | PATIENTS AND METHODS

2.1 | Participants and data

A de-identified database of clinical information on was generated from 2003 to 2013 at the National Institute of Aging (NIA) (#03-AG0N330, formerly 2003–86, now included in #11-AGNO79), as part of the natural history study of heritable disorders of connective tissue.

There were 1,010 participants in the study in total with various connective tissue disorders, 328 of whom had non-vascular EDS. The original project and the analyses included in this study both were approved by the NIA Institutional Review Board (IRB), and informed consent was obtained from each participant. Participants in the NIA study were referred from centers throughout the United States and evaluated systematically by one co-investigator (CF). Laboratory data, physical exams, and several surveys were available on the children. Surveys were filled out by the participants; younger participants may have had help from parents. Once the project was closed, the NIA IRB approved release of the de-identified data from the study to interested investigators for future analysis. The current project was also approved by the IRBs at both the Johns Hopkins University School of Medicine and the Greater Baltimore Medical Center. Ultimately 72 patients from this database were eligible and based on exclusion criteria (see below) 41 were included in the analysis (Figure 1).

Data drawn from the patient's complete medical records included demographic information, Beighton score (completed in standardized manner with a goniometer), other medical diagnoses, physical exam findings, and family history. The cohort was chosen based on a confirmed or suspected diagnosis of non-vascular EDS, age (18 years and younger), and Beighton score of 4/9 or higher. Participants were excluded if no Beighton score was recorded. At the time of the NIA project, the 1997 Villefranche criteria were the accepted diagnostic criteria for Ehlers–Danlos syndrome (Beighton et al., 1998). Although major and minor criteria were defined for each of the subgroups, the precise number of each criteria necessary to establish the diagnosis were not specified. Testing for classical EDS was strongly suggested and criteria for vascular EDS were more specific (“the presence of any two or more of major criteria is highly indicative of the diagnosis”). The geneticists at the NIA, including one author (CF), determined that in the presence of other findings including skin involvement and complications of joint hypermobility, a Beighton score of 4 was acceptable for a diagnosis of hypermobile and classical types. This is in keeping with the paper by Tinkle et al., published before the NIA project ended, stating that joint hypermobility syndrome and hypermobile EDS were one and the same entity (Tinkle et al., 2009). A Beighton score of greater than 4 is the typical cutoff for defining joint hypermobility based on the Brighton criteria (Grahame et al., 2000), while the cutoff for EDS based on the Villefranche criteria is 5 or greater. Participants who had joint hypermobility and skin findings but did not meet the clinical criteria for classical or hypermobile EDS and did not fit into any other defined hereditary disorder of connective tissue (including other types of EDS, Marfan syndrome, Stickler syndrome, Loeys–Dietz syndrome), were classified as “EDS-unspecified” (uEDS).

According to the new 2017 criteria (Malfait et al., 2017), these would now likely be considered to have hypermobility spectrum disorder, but at the time the geneticists, including one author (CF), used “unspecified”. None of the participants had molecular testing prior to entry into the study.

2.2 | Questionnaires

Participants completed the Brief Pain Inventory (BPI) and the Pittsburgh Sleep Quality Index (PSQI). Several other questionnaires were provided to the participants but completion rates were low. Therefore, results from these measures were used as the primary outcomes for statistical analysis. Both the BPI (Batqalha & Mota, 2013; Barney et al., 2013) and the PSQI (Ayaki et al., 2016; Noone et al., 2014; Yuksel et al., 2007) have been utilized in pediatric populations.

The PSQI (Buysse et al., 1989) asks nineteen questions regarding seven components of sleep over the past month (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction), which are summed to create a global score of sleep quality (range = 0–21), with higher scores indicating lower quality sleep. Individual components of the score range from 0 to 3, with 3 being the worst quality sleep. A global PSQI score greater than five suggests significant sleep concerns (Buysse et al., 1989).

The short form of the BPI was used (Cleeland & Ryan 1994), which has nine items. Initially used to assess cancer pain, the BPI is now used for other chronic pain conditions. The survey produces two scores: a pain severity score and a pain interference score. For the pain severity score, the respondent answers four questions relating to worst in the last week, least, average, and current pain. Zero correlates with no pain and 10 with the worst pain a person can imagine. For pain interference, seven questions are asked about how pain interferes with general activity, mood, walking ability, normal walk, relations with other people, sleep, and enjoyment of life. A score of 0 means that pain does not interfere, and a score of 10 means that pain completely interferes. The final score from the survey for the pain severity score is out of 40, and for the pain interference score is out of 70; a higher score correlates with more severe pain and higher interference from pain, respectively (Poquet et al., 2016). As a significant proportion of participants left either one or two questions unanswered, we evaluated the average of the responses rather than the total score.

2.3 | Statistical analysis

We used descriptive statistics to summarize participant characteristics. BMI and BMI centiles were calculated according to standard CDC growth charts (Kuczmarski et al., 2000). We compared normally distributed ordinal data using *t*-tests, and nominal or categorical data using Mann–Whitney U test, Chi-square tests or Fisher exact tests as appropriate. We conducted linear regressions to determine correlations between outcomes. All analysis was done using the R 3.4.1 software program. We considered a probability (*p*) value of less than 0.05 as statistically significant for this exploratory study.

3 | RESULTS

3.1 | Study population

From the 72 pediatric participants in the NIA study, 41 were eligible for this analysis, as shown in Figure 1. Most exclusions were due to either a low or unavailable Beighton score. Except for two participants for whom ethnicity was not provided, all participants were

Caucasian. Table 1 provides the demographic and clinical characteristics of the 41 included participants (13 male and 28 female), as well as the 25 who completed the PSQI and the 24 who completed the BPI. The mean age was 12.9 and 14.5 years for males and females, respectively. There was no significant difference in proportion of males and females with in each diagnostic category (hEDS, cEDS, uEDS). There was no significant difference between males and females in age or BMI. Females had a higher mean Beighton score than males (7.4 vs. 6.3, mean difference 1.1, 95% CI 0.1–2.1, $p = 0.02$).

3.2 | BPI data

The BPI scores are displayed in Table 2. There were no differences in age, sex, BMI, or type of EDS between the 24 who completed the BPI and the 17 who did not. The average pain severity and interference scores were 3.7 ± 2.3 and 3.7 ± 2.8 , respectively. Males and females scored an average of 4.2 and 3.6, respectively, for the BPI severity score and 4.6 and 3.5 for the BPI interference score. Statistical significance between male and female BPI scores could not be assessed due to the limited number of male participants.

3.3 | PSQI data

Average global PSQI scores are displayed in Table 2. No effect was observed from age, sex, BMI, or type of EDS. Females had a higher average PSQI score ($p = 0.02$) than males. Mean PSQI scores were 2.6 for males and 5.7 for females (mean difference 3.1, 95% CI 0.76–5.5, $p = 0.01$). While this difference was statistically significant, there were only 7 male respondents for the PSQI. 9/23 (39.1%) had a PSQI ≥ 5 meeting the cutoff for “poor sleeper” (1/3 of those with cEDS, 4/7 with hEDS, and 4/13 with uEDS).

3.4 | BPI versus PSQI

There were 16 participants who completed both the BPI and PSQI. As illustrated in Figure 2, BPI severity and interference scores correlate with each other ($r^2=0.37$; $p < 0.01$). Neither pain severity or interference correlated with PSQI score ($r^2=0.02$, $p = 0.23$ and $r^2=0.11$, $p = 0.66$ respectively) (Figure 2). We conducted a comparison of the Beighton = 4 to the Beighton ≥ 5 groups. The group with Beighton = 4 had lower mean BPI severity scores (1.0 vs. 3.9, mean difference 2.9, 95% CI 0.44–3.9, $p < 0.02$), otherwise there was no significant difference in any other measure between the groups (Mann–Whitney U test). We compared the results of the study as conducted ($n = 41$, Beighton ≥ 4) to the study if those with a Beighton = 4 were removed ($n = 36$, Beighton ≥ 5). The removal of those five patients with a Beighton of four did not significantly change any result (Mann–Whitney U test).

4 | DISCUSSION

Many centers have been evaluating the diagnostic criteria, natural history, associated complications, and underlying cause(s) of the Ehlers–Danlos syndromes. The goal of this study was to expand the literature describing factors affecting quality of life in children with non-vascular EDS and to define factors impacting quality of life metrics, ultimately improving clinical care. The main findings of this study were that pain interference and severity scores correlated with each other but not with sleep quality, and that females had worse sleep quality than males.

Pain is common in children with joint hypermobility (Leone et al., 2009; McCluskey et al., 2012; Tobias et al., 2013) and in children with hypermobility EDS (Scheper et al, 2017a, Stern et al., 2017), although there is considerable heterogeneity between studies (McCluskey et al., 2012). Our non-vascular EDS patients had mean BPI pain severity scores of 3.7 ± 2.3 and mean BPI pain interference scores of 3.7 ± 2.8 (Table 2). While no study that we are aware of has utilized the BPI to evaluate patients with EDS, our scores were better than adult patients with various medical problems referred to a chronic pain center (severity score 9.9 ± 1.8 , interference score 7.6 ± 2.0 , Tan, 2004) but worse than adults with myotonic and fascioscapulohumeral dystrophy (severity 4.4 and interference 2.9, Jensen et al., 2008). The BPI was acceptable and internally consistent, suggesting its utility for pain measurement in future EDS studies. Our study population's mean global PSQI of 7.0 ± 1.7 is comparable to other chronic medical conditions (range 4.1–6.3) (Yuksel et al., 2007; Fauroux et al., 2012) and worse than healthy children (range 1.1–4.9) (Üçer & Gümüş, 2014; Noone et al., 2014). The fact that 39.1% of our patients' had a PSQI greater than five suggests that problems with sleep quality may be common in children with non-vascular EDS.

While there have been several studies that have reported on the correlation between pain and fatigue in EDS, to our knowledge only one study has evaluated sleep quality in patients on the joint hypermobility/EDS disease spectrum. Albayrak et al. (2015) observed worse sleep quality, more pain, and fatigue, in adults with benign joint hypermobility syndrome (BHJS) in comparison to controls. In contrast to our findings, there was a positive correlation between sleep quality and pain scores. In general, sleep quality is one of the primary factors contributing to fatigue and the two have been shown to correlate with each other (Ghaem & Haghighi 2008; Lavidor, Weller & Babkoff 2003). That our study did not find a correlation between sleep quality and pain severity could be due to the differences in populations studied, specifically children with non-vascular EDS in our study versus the assessment of adults with BHJS by Aybarak et al. Data from a Dutch cohort of adults with various types of EDS found correlations between fatigue and pain severity, functional impairment, and muscle weakness (Voermans et al., 2010a; Voermans et al., 2010b; Voermans et al., 2011). Other studies have found significant associations between pain severity and fatigue severity in adults with EDS (Krahe et al., 2017; De Wandele et al., 2016). While there is evidence that adults and children do not differ in some outcome measures (Scheper et al., 2017), our findings suggest there may be important differences. In line with our findings, a previous report on the first 65 patients of all ages enrolled in the NIA study showed that of patients with a PSQI score >5 , only 48% reported generalized pain (Mandel et al., 2006).

The literature supports that females with EDS often have worse disease morbidity than males with EDS. Studies of adult populations have shown that in comparison with their male counterparts, females have lower pain pressure thresholds (Scheper et al., 2017b), more frequent cutis laxa, striae, enamel discolorations, resistance to local anesthetics (Castori et al., 2015), tendinopathy, hip impingement, weakness/deconditioning, and contusions (Stern et al., 2017), and higher numbers of complaints and severity per complaint (Maeland et al., 2011). Interestingly, Scheper et al. (2017a) in a pediatric EDS population found that while females had more painful joints and higher pain severity, they had less fatigue than males. We are unable to fully comment on male/female differences in pain and sleep quality due to the small number of male participants, though higher Beighton scores were found in

females. Similarly, while the comparison of participants with a Beighton score of 4 versus those with a score 5 found a small difference in pain severity and no other differences, the small number of participants in the former group ($n = 5$) precludes generalizable inferences.

This study has several limitations which can be addressed by future work. As a result of the retrospective exploratory study design, there was a small sample size and many participants did not complete all of the surveys fully enough for them to be scored. Since the participants were all Caucasian, these results may not necessarily be generalizable to all populations of children with EDS. Information on socioeconomic status was not collected which could confound the results. The large body of historical data on the surveys analyzed helps account for the absence of a control group. There was only one time-point during which the data was obtained for the majority of the patients, so longitudinal analysis was unable to be conducted. The lack of a specific measure of fatigue is another limitation. Finally, as this is a survey-based study, it is susceptible to recall bias. While the lack of a control group and low number of patients limit the extent to which conclusions can be firmly drawn from these data, we believe that these results can help direct future research. These results could reflect upon the quality of life of a larger population of children with non-vascular EDS. Future research will focus on development of a brief questionnaire-based tool to risk stratify pediatric patients with EDS, better assess areas affecting quality of life, and identify those patients potentially needing earlier intervention or diagnostic testing.

In conclusion, we confirm that pain and sleep are significant problems in pediatric patients with non-vascular EDS. Contrary to the established literature in other disease populations, we found no correlation between pain severity or interference and sleep quality. Evaluating and monitoring pain and sleep quality is an important part of pediatric EDS management, and could lead to improved patient-directed and individualized therapies. Early testing and screening, with prompt intervention is important to improve quality of life and function in pediatric non-vascular EDS across the lifespan at a time where intervention is most helpful. The primary limitation of this study is small sample size. Further work to develop clinical tools such as focused surveys to improve early identification and management of pediatric patients with non-vascular EDS, are at higher risk for worse outcomes and poor quality of life, is ongoing.

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FIGURE 1.

Exclusion criteria and final number of participants [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 2.
Comparison of BPI and PSQI scores

TABLE 1

Participant demographics and characteristics. Mean, standard deviation (SD) and range are reported for participants' age in years and body mass index (BMI) centile. Median and range are reported for Beighton score. Participant sex and type of Ehlers–Danlos Syndrome (EDS) are reported as number of participants and percent of the total. These characteristics are divided by participants who answered the Pittsburgh Sleep Quality Index (PSQI), Brief Pain Inventory (BPI), and all participants

	PSQI		BPI		Total	
	Mean/ median	SD	Range	Mean/ median	SD	SD
Age (years)	14.9	2.52	7–18	15.3	2.16	3.6
BMI centile	57.6	26.3	0.78–99.4	57.5	24.4	27.2
Beighton score	8/9		4–9	8/9	4–9	7/9
		n (%)			n (%)	n (%)
Male		8 (32.0)			4 (16.7)	13 (31.7)
Female		17 (68.0)			20 (83.3)	28 (68.3)
EDS-Classical		3 (12.0)			3 (12.5)	6 (14.6)
EDS-Hypermobility		9 (36.0)			8 (33.3)	10 (24.4)
EDS-unspecified		13 (52.0)			13 (54.2)	25 (61.0)

TABLE 2

Results of BPI and PSQI surveys, with standard deviation, range, and mean

	Boys			Girls			Total		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
BPI severity score	4.19	1.75	2.50–6.25	3.63	2.46	0–10	3.73	2.33	
BPI interference score	4.59	1.49	3.57–6.80	3.50	2.94	0–9.43	3.69	2.75	
PSQI global score	2.57	1.81	0–6	5.69	3.61	1–14	4.74	3.45	