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Sleep Fragmentation and Biomarkers in Juvenile Idiopathic Arthritis

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Abstract

Objectives: (1) To compare sleep (nighttime sleep duration and sleep efficiency) and sleep fragmentation (movement and fragmentation index), as measured by actigraphy, and symptoms (pain and fatigue) in 8- to 14-year-old children with polyarticular and extended oligoarticular juvenile idiopathic arthritis (JIA) and (2) to examine the associations between sleep fragmentation (movement and fragmentation index) and the calcium-binding protein biomarkers S100A12 and myeloid-related protein (MRP8/14). **Method:** Participants included 40 children with extended oligoarticular ($n = 15$) or polyarticular ($n = 25$) JIA and their parents. Serum protein samples were obtained during routine rheumatology clinic visits. Children completed the PedsQL Multidimensional Fatigue Scale and daily pain and sleep diaries and wore actigraphy monitors for 9 consecutive days. Parents completed the Children's Sleep Habits Questionnaire (CSHQ). **Results:** Of the 40 children, 68% scored above the CSHQ clinical cutoff score for sleep disturbances. Mean nighttime sleep duration was 7.5 hr, and mean sleep efficiency was 85.3%. Group differences were not found for nighttime sleep duration, sleep efficiency, movement and fragmentation index, or S100A12 and MRP8/14 protein concentrations. In a stepwise regression, medications, joint count, and movement and fragmentation index explained 21% of the variance in MRP8/14 concentration. **Conclusion:** Decreased nighttime sleep duration, poor sleep efficiency, and fragmented sleep were observed in our sample, regardless of JIA category. Sleep fragmentation was a significant predictor of MRP8/14 protein concentration. Additional research is needed to understand the interrelations among sleep fragmentation, effects of medication, and S100A12 and MRP8/14 protein biomarkers in JIA.

Keywords

actigraphy, juvenile idiopathic arthritis, MRP8/14, S100A12 proteins, S-calprotectin, sleep fragmentation, CSHQ

An estimated 300,000 children in the United States have some form of rheumatic disease, the most common of which is juvenile idiopathic arthritis (JIA; Ilowite, 2002; Minden, 2009; Sacks, Helmick, Luo, Ilowite, & Bowyer, 2007). JIA can persist into adulthood and result in significant long-term morbidity and disability (Bowyer et al., 2003; Minden et al., 2002; Selvaag et al., 2006). Disease severity varies, with unpredictable episodes of joint inflammation, pain, stiffness, and limited mobility, followed by episodes of inactive disease. Children with polyarticular JIA ($\geq$5 joints involved at the time of diagnosis) and those with extended oligoarticular JIA (<5 joints involved during the first 6 months of disease with involvement of $\geq$5 joints thereafter) have particularly refractory disease and worse health outcomes (i.e., lower health-related quality of life), and thus they were the focus of the present pilot study (Ringold, Ward, & Wallace, 2013; Wallace, Huang, Bandeira, Ravelli, & Giannini, 2005).

In comparison with healthy peers, children with JIA report more fatigue (Ringold et al., 2013) and sleep fragmentation (Bromberg, Gil, & Schanberg, 2012; Butbul Aviel et al., 2011; Lopes et al., 2008; Passarelli et al., 2006; Ruperto et al., 2010; Ward et al., 2008; Zamir, Press, Tal, & Tarasiuk, 1998). Sleep fragmentation, defined as increased movement, arousals, and restlessness during sleep, results in inadequate amounts of sleep. Fragmented sleep may be secondary to underlying sleep disorders (e.g., sleep-disordered breathing and

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periodic limb movement disorder), symptoms of pain and inflammation, and/or poor sleep habits. Passarelli and colleagues (2006) found that, compared to healthy controls, children with JIA had reduced nighttime sleep duration, more arousals, and increased periodic limb movements. Lopes et al. (2008) reported increased arousals and increased cyclic alternating patterns during deep sleep in children with JIA but not in a comparison group of children. In our previous study, we found that 40% of children with JIA had mild sleep-disordered breathing indicative of sleep fragmentation, regardless of pain levels and whether the disease was active or inactive (Ward et al., 2010).

The underlying mechanisms of sleep fragmentation in JIA are not well understood and have not been explored in a comprehensive manner. In the present study, we examine the calcium-binding proteins S100A12 and myeloid-related protein 8/14 (MRP8/14), which have been found to correlate with inflammation and predict clinical response to treatment in JIA (Choi et al., 2015; Foell et al., 2004, 2010; Frosch et al., 2003; Wittkowski et al., 2011). These proteins are expressed in myeloid cells and secreted by activated phagocytes under various inflammatory conditions, including JIA, atherosclerosis, and irritable bowel disease (Foell et al., 2003; Leach et al., 2007; Yui, Nakatani, & Mikami, 2003). S100A12 and MRP8/14 serum protein concentrations have also been associated with fragmented sleep, including sleep-disordered breathing, in both children and adults without JIA (Bhattacharjee et al., 2012; Kim et al., 2010; Shi, Chen, Huang, & Li, 2013). Sleep fragmentation secondary to increased arousals and hypoxia can result in inflammation and disruption in normal ventilation and oxygenation. To our knowledge, the associations between S100A12 and MRP8/14 concentrations and sleep fragmentation have not been evaluated in children with JIA.

The aims of this study were to (1) compare sleep (nighttime sleep duration and sleep efficiency) and sleep fragmentation (movement and fragmentation index), as measured by actigraphy, and symptoms (pain, fatigue) in 8- to 14-year-old children with polyarticular and extended oligoarticular JIA and (2) examine the associations between sleep fragmentation (movement and fragmentation index) and the calcium-binding protein biomarkers S100A12 and MRP8/14 in these children. Given our previous findings regarding sleep in JIA (Ward et al., 2008, 2010), we hypothesized that children with JIA would show decreased nighttime sleep duration, decreased sleep efficiency, increased movement and fragmentation index score, and increased fatigue, regardless of JIA category or disease state (active vs. inactive). Based on the previous studies of S100A12 and MRP8/14 serum protein concentrations and sleep fragmentation (Bhattacharjee et al., 2012; Kim et al., 2010), we hypothesized that the movement and fragmentation index score would be positively associated with S100A12 and MRP8/14 serum protein concentrations. Given the developmental age–related changes in sleep, we also compared sleep and sleep fragmentation indices in 8- to 11-year-old children to those in children aged 12–14 years.

Method

Participants

We obtained approval for this study from the institutional review board at Seattle Children's Hospital. Children aged 8–14 years were eligible if they met the Edmonton International League of Associations for Rheumatism criteria (2nd revision) for a diagnosis of polyarticular JIA (rheumatoid factor positive or negative) or extended oligoarthritis. We recruited 40 children who fulfilled these criteria from the hospital's rheumatology clinic. During a routine clinic visit, a rheumatologist informed the parent and child about the study, and if they were interested, a trained research coordinator explained the purpose of the study and obtained consent and assent. Children were excluded if they had a psychiatric condition (e.g., attention-deficit hyperactive disorder and depression), a family history of narcolepsy, or a chronic condition (e.g., Down syndrome, craniofacial disorders, and asthma) or were unable to complete the English-language versions of the assessment questionnaires.

General Procedures

During the research visit, children were admitted to the Pediatric Clinical Research Center, and we obtained their height and weight measures and their blood sample. Children and parents completed questionnaires, and we gave children an actigraph and sleep diary. A pediatric rheumatologist examined the child and rated disease activity (Physician Global Assessment [PGA]), with active disease defined as inflammation of one or more joints, active uveitis (swelling or irritation of the uvea), and PGA score $\geq$1 on a scale of 0–10). Inactive disease was defined as no inflamed joints, PGA = 0, morning stiffness for a duration of $\leq$15 min, erythrocyte sedimentation rate $\leq$20 mm/hr, C-reactive protein <0.8, and no active uveitis (Brewer et al., 1977; Cassidy et al., 1986; Wallace, Giannini, Huang, Itert, & Ruperto, 2011).

Sleep

Children's Sleep Habits Questionnaire (CSHQ). The CSHQ is a parent-report questionnaire used to examine sleep patterns and sleep problems in children (Owens, Spirito, & McGuinn, 2000). The CSHQ consists of eight subscales: bedtime resistance, sleep-onset delay, sleep duration, sleep anxiety, night awakenings, parasomnias, sleep-disordered breathing, and daytime sleepiness. Parents report on the child's typical sleep behaviors over the past week and indicate whether or not a particular sleep behavior was problematic by circling *yes* or *no.* Item responses are rated on a 3-point scale for frequency of sleep behavior: *usually* = 5–7 times per week, *sometimes* = 2–4 times per week, and *rarely* = 0–1 time per week (Wallace et al., 2011). The CSHQ yields a total sleep disturbance score and eight subscale scores. A total sleep disturbance score >41 is a clinical indicator of disturbed sleep. Investigators have used the CSHQ in previous studies involving children with JIA

and typically developing school-age children (Bloom et al., 2002; Butbul Aviel et al., 2011; Ruperto et al., 2010; Ward et al., 2008). Reliability of the total sleep disturbance score in this sample was $\alpha = .81$.

Actigraphy. Each child wore an actigraph (Actiwatch 64; Mini-Mitter Philips Respironics, Bend, OR) on the nondominant wrist for 9 consecutive days. We instructed the parent and child in the application of the monitor, including removal during bathing or swimming. Actiwatch 64 has an accelerometer that senses the occurrence and degree of motion in all directions. It converts this motion into an electrical signal and stores it as an activity count. We collected actigraphy data in 1-min epochs and analyzed them with the Actiware, Version 5.04, software. We used sleep diary data for bedtime and risetime and event markers to calculate sleep–wake variables. Actigraphy sleep outcome variables of interest were (1) nighttime sleep duration defined as the number of minutes scored as sleep between sleep onset and sleep offset during the sleep interval (similar to polysomnography [PSG] sleep period time), (2) sleep efficiency defined as the ratio of total sleep time/time in bed, (3) wake after sleep onset defined as the percentage of scored total wake time during the sleep interval multiplied by 100, and (4) movement and fragmentation index defined as a measure of movement and brief immobility intervals (<1 min), with higher values indicative of more restlessness during sleep. Actigraphy is a valid and reliable measure of sleep that has been used in pediatric populations (Acebo et al., 1999; Law, Dufton, & Palermo, 2012; Sadeh, Haurim, Kripke, & Lavie, 1995; Ward, Lentz, Kieckhefer, & Landis, 2012). Actigraphy data were available for 38 children, and we used averaged sleep variables in analyses. Actigraphs malfunctioned for two children.

Sleep diary. Children documented in their daily sleep diary the time they went to bed each night, the time they awoke each morning, the number and duration of night awakenings, and the number and duration of naps. In addition, they recorded evening activities, caffeine consumption, medications (type, dosage, and frequency), illness, and whether or not they went to school. Children also recorded periods during which they were not wearing the actigraphy monitor. We instructed parents to push the event marker on their child's actigraph at bedtime and wake time. At the end of the 9-day monitoring period, we downloaded data from each actigraphy. We contacted participants by telephone midweek to answer any questions they might have.

Fatigue

The PedsQL Multidimensional Fatigue Scale is an 18-item, age-specific parent/proxy report assessment of a child's fatigue during the last month. This scale includes three subscales: general fatigue, sleep/rest fatigue, and cognitive fatigue. Survey items are rated on a 5-point scale (0 = *not at all a problem* and 4 = *a significant problem*). Items are reverse scored on a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0), with higher scores indicating less fatigue (better health-related quality of life). A total fatigue score is also calculated based on the summation of the three subscale scores. Previous studies established the reliability and validity of the PedsQL Multidimensional Fatigue in children aged 2–18 years with JIA (Ringold et al., 2013; Varni, Burwinkle, & Szer, 2004).

Biomarkers

We collected and processed the serum samples in the Pediatric Clinical Research Center. S100A12 and MRP8/14 serum concentration levels were measured by a double-sandwich enzyme-linked immunosorbent assay system established in Muenster, Germany, the method for which has been previously described (Foell et al., 2003; Schulze zur Wiesch et al., 2004). The inter- and intra-assay coefficients of variation for this assay are <9% and 8% ($n = 10$), respectively.

Medications

Any medications participating children took during the study period were indicated on a questionnaire with *yes* or *no* and classified into the following categories: (1) disease-modifying antirheumatic drugs (DMARDs; e.g., methotrexate and arava), (2) sulfasalazine, (3) biologics (e.g., enbrel), (4) nonsteroidal anti-inflammatory drugs, (5) corticosteroids, (6) other (e.g., vitamins and folic acid), and (7) none.

Statistical Analysis

Group differences between children with extended oligoarticular and polyarticular JIA were computed on demographic (age and sex) and clinical variables (disease condition, PGA, medications, count of affected joints, and fatigue) using χ^2tests for categorical variables and *t*-tests for continuous variables. We examined the data on S100A12 and MRP8/14 protein levels for outliers, defined as values >2 *SD*s from the mean, and excluded three children from these analyses on that basis. S100A12 and MRP8/14 concentration data were skewed; therefore, we logarithmically transformed them. We conducted Spearman's correlation analyses to examine the associations among serum concentration of the protein biomarkers, clinical variables (PGA, joint count, and fatigue), and sleep (CSHQ sleep disturbances, actigraphy sleep [nighttime sleep duration and sleep efficiency], and sleep fragmentation [movement and fragmentation index]). To address the first aim, we examined group differences in clinical characteristics and sleep (CSHQ sleep disturbances, actigraphy sleep [nighttime sleep duration and sleep efficiency], and sleep fragmentation [movement and fragmentation index]) between children with polyarticular and extended oligoarticular JIA. Because of the developmental age–related changes in sleep with age, we also examined sleep (CSHQ sleep disturbances, actigraphy sleep [nighttime sleep duration and sleep efficiency], and sleep fragmentation [movement and fragmentation index]) by age-group (8–11 years and 12–14 years). To address the second aim, we examined

Table 1. Demographic and Clinical Characteristics of Participating Children With JIA.

Characteristic	Polyarticular JIA ($n = 25$)	Extended Oligo ($n = 15$)	95% Confidence Interval of the Difference
Age, years, mean ± *SD*	11.5 ± 1.9	11.4 ± 1.8	[−1.3, 1.1]
Sex, female, *n* (%)	19 (76%)	12 (80%)	
Disease condition, active, *n* (%)	13 (52%)	9 (60%)	
Age at diagnosis, years, mean ± *SD*	7.4 ± 3.4	5.4 ± 3.9	[−4.4, 0.34]
PGA, mean ± *SD*	1.4 ± 1.9	1.2 ± 1.4	[−1.3, 0.91]
Medications, *n* (%)			
DMARDS (arava and methotrexate)	18 (72%)	9 (60%)	
Sulfasalazine	0 (0%)	1 (6.7%)	
Biologics (enbrel, remidcade, and humira)	10 (40%)	6 (40%)	
NSAIDS	14 (56%)	6 (40%)	
Corticosteroids	1 (4%)	4 (26.7%)	
None	1 (4%)	2 (13.3%)	
Pain, joint count, mean ± *SD*	3.6 ± 7.0	1.4 ± 2.3	[−5.4, 0.87]
Fatigue,[a] mean ± *SD*			
Total fatigue	76.8 + 20	83.0 + 17	[−6.8, 19.3]
Sleep/rest	75.8 ± 21	75.3 ± 24	[−15.7, 14.8]
Cognitive	73.8 ± 22	85.4 ± 16	[−2.1, 25.3]
General	79.5 ± 21	88.4 ± 16	[−4.1, 21.9]
Protein biomarker concentration, mean ± *SD*			
S100A12 (ng/ml)	78.6 ± 50	73.9 ± 42	[−38.3, 28.9]
Logged S100A12	4.2 ± .58	4.2 ± .55	[−0.44, 0.37]
MRP8/14 (ng/ml)	699.1 ± 407	686.2 ± 348	[−286.6, 260.1]
Logged MRP8/14	6.4 ± .54	6.4 ± .53	[−0.38, 0.38]

Note. JIA: juvenile idiopathic arthritis; DMARDS = disease-modifying antirheumatic drugs; extended oligo = extended oligoarticular JIA; MRP8/14 = myeloid-related protein; NSAIDS = nonsteroidal anti-inflammatory drugs; PGA = Physician Global Assessment.
[a]Fatigue was measured with the PedsQL Multidimensional Fatigue Scale.

relationships among log-transformed protein biomarker concentrations, sleep fragmentation (movement and fragmentation index), and clinical characteristics (disease condition, medication, joint count, and fatigue) with a series of stepwise regression models. We explored how much of the variance in S100A12 and MRP8/14 levels was explained by medication, joint count, and sleep fragmentation (movement and fragmentation index). To control for multiple comparisons, we set p values at <.01 (two tailed). We analyzed data using SPSS for Windows, Version 17.0 (SPSS Inc., Chicago, IL).

Results

Clinical Characteristics

Table 1 shows the clinical and demographic characteristics of the children with extended oligoarticular and polyarticular JIA. The average age for the entire sample was 11.5 ± 1.8 years. Children with extended oligoarticular and polyarticular JIA did not differ by age, sex, joint pain, fatigue, or S100A12 and MRP8/14 concentrations.

Sleep

Among the participants as a whole, 68% of the children scored above the CSHQ clinical cutoff score of 41. The CSHQ subscales did not differ by type (extended oligoarticular vs. polyarticular) or state (active vs. inactive) of JIA. Mean nighttime sleep duration was 7.5 hr, and mean sleep efficiency was 85.5%. We did not find group differences (type of disease) for any of the actigraphy sleep or sleep fragmentation measures.

Table 2 shows CSHQ scores and actigraphy sleep variables by age-group. Neither the CSHQ subscale nor the total score differed by age-group. However, we found significant age-group differences for nighttime sleep duration ($t = 3.3$, $p < .003$) and sleep onset (i.e., bedtime; $t = -2.1$, $p < .04$) as measured by actigraphy, such that the 8- to 11-year-old children slept 37 min longer and went to bed 31 min earlier than the 12- to 14-year-old children.

Predictors of Protein Biomarkers

We found no associations among age, JIA category, disease condition, protein concentrations, or symptoms (joint count and fatigue). MRP8/14 was inversely associated with taking DMARDs ($r = -.56$, $p < .05$). We controlled for medications and join count because children with polyarticular JIA were on more medications and had higher joint counts than children with extended oligoarticular JIA. In the regression models, we entered medication and joint count in the first step and movement and fragmentation index in the second step. In the first regression model, medication, joint count, and movement and fragmentation index explained 21% of the variance in MRP8/14 concentration, $F(3, 35) = 3.5$, $p = .02$ (Table 3). Table 4 shows the second regression model, in which medication, joint count, and

Table 2. Parent-Reported CSHQ and Actigraphy Sleep Variables by Age-Group.

Variable	8–11 years ($n = 16$)	12–14 years ($n = 24$)	95% Confidence Interval of the Difference
CSHQ			
Bedtime resistance	6.7 ± 1.8	6.9 ± 1.3	[−1.1, 0.81]
Sleep-onset delay	1.6 ± 0.63	1.5 ± 0.66	[−.33, 0.53]
Sleep duration	3.9 ± 0.99	4.3 ± 1.6	[−1.2, 0.47]
Sleep anxiety	5.2 ± 1.9	4.2 ± 1.1	[−.07, 2.1]
Night wakings	4.4 ± 1.5	3.7 ± 1.0	[−.09, 1.7]
Parasomnias	9.6 + 2.7	8.1 + 1.1	[−.02, 2.9]
Sleep-disordered breathing	3.0 ± 0.63	3.1 ± 0.42	[−.43, 0.25]
Daytime sleepiness	14.2 ± 3.5	12.6 ± 3.3	[−.66, 3.8]
Total sleep disturbance	47.9 ± 8.9	43.1 ± 7.6	[−.52, 10.1]
CSHQ score > 41,[a] *n* (%)	13 (81%)	14 (58.3%)	
Actigraphy			
Sleep onset, hr*	22:32 ± 0:25	23:06 ± 0:22	[−1.3, −0.4]
Sleep offset, hr	07:51 ± 0:21	07:45 ± 0:18	[−0.50, 0.59]
Nighttime sleep duration, min**	469.5 ± 10.1	431.5 ± 8.7	[11.6, 53.3]
Sleep efficiency, %	85.3 ± 1.0	85.8 ± 0.9	[−2.9, 2.9]
Wake after sleep onset, min	73 ± 19	67 ± 25	[−9.6, 21.9]
Movement and fragmentation index	89.7 ± 7.9	94.2 ± 9.6	[−10.6, 1.6]

Note. Data are reported as mean ± *SD*, unless otherwise indicated. CSHQ = Children's Sleep Habits Questionnaire.
[a]Scores >41 on the CSHQ are considered a clinical indication of disordered sleep.
*$p < .05$. **$p < .005$.

Table 3. Effect of Sleep Fragmentation on Myeloid-Related Protein (MRP8/14) Concentration.

	Stepwise Regression						
	R^2_{change}	F_{change}	R^2_{total}	R^2_{Adj}	F_{total}	*b* (*SE*)	*t*
Log-MRP8/14							
Step 1	.06	0.96 (2, 30)*	.06	.14	0.96 (2, 32)		
Intercept***						6.70 (.30)	22.10
Medication						−.38 (.32)	−1.21
Joint count						.03 (.32)	.80
Step 2	.21	8.16 (1, 29)*	.27	.18	3.51 (1, 30)*		
Intercept***						4.1 (.95)	4.30
Medication						−.47 (.29)	−1.64
Joint count						.05 (.03)	1.69
Movement and fragmentation index**						.03 (.01)	2.86

Note. $n = 35$.
*$p < .05$. **$p < .01$. ***$p < .001$.

movement and fragmentation index explained 10% of the variance in S100A12 concentration, but the overall model was not significant, $F(3, 35) = 2.9$, $p = .052$.

Discussion

In the present sample, 68% of children with JIA scored above the CSHQ clinical cutoff score for disordered sleep, a finding that is similar to those of previous studies (Bloom et al., 2002; Butbul Aviel et al., 2011; Ruperto et al., 2010; Ward et al., 2008). Average nighttime sleep duration was well below 8.5–10 hr the National Sleep Foundation recommends for youth. Despite the fact that we measured sleep in the home environment over 9 consecutive days, we observed high levels of sleep fragmentation and poor sleep efficiency, an index of sleep quality, regardless of JIA subtype and disease state. These findings suggest that these children had an accumulated sleep debt that could be attributed to poor sleep hygiene and/or untreated or unrecognized sleep disorders such as sleep-disordered breathing or periodic limb movements. In our previous studies, 40% of children with JIA had unrecognized and untreated sleep-disordered breathing, as measured by PSG (Ward et al., 2010). CSHQ sleep disturbance score and subscale scores and actigraphic sleep variables did not differ significantly between children with extended oligoarticular and polyarticular JIA in the present study, a finding similar to those of previous studies (Butbul Aviel et al., 2011; Ruperto et al., 2010; Ward et al., 2008, 2010). Parent-reported sleep

Table 4. Effect of Sleep Fragmentation on S100A12 Concentration.

	Stepwise Regression						
	R^2_{change}	F_{change}	R^2_{total}	R^2_{Adj}	F_{total}	*b* (*SE*)	*t*
Log-S100A12							
Step 1	.13	2.20 (2, 30)*	.13	.07	2.20 (2, 32)		
Intercept***						4.75 (.31)	15.50
Medication*						−.67 (.32)	−2.08
Joint count						.02 (.03)	.51
Step 2	.10	3.85 (1, 29)*	.23	.15	2.89 (1, 31)*		
Intercept***						2.82 (1.02)	2.76
Medication*						−.73 (.31)	−2.37
Joint count						.04 (.03)	1.09
Movement and fragmentation index						.02 (.01)	1.96

Note. $n = 35$.
*$p < .05$. ***$p < .001$.

disturbances and actigraphic sleep measures also did not differ by disease state (data not shown), which is consistent with our previous studies (Ward et al., 2008, 2010). Movement and fragmentation index was a significant predictor of MRP8/14, but not S100A12, protein concentration.

Our findings partially support our hypothesis, as the fragmentation and movement index was a significant predictor of MRP8/14, but not S100A12, protein concentration. These calcium-binding proteins are secreted by phagocytes under inflammatory conditions (Rammes et al., 1997), including cardiovascular disease and sleep-disordered breathing, a measure of sleep fragmentation (Bhattacharjee et al., 2012; Kim et al., 2010). MRP8/14 and S100A12 may have different rates of posttranslational modification that contribute to changes at their binding sites, which may explain why we did not find that their expression varied together (Augner, Eichler, Utz, & Pischetsrider, 2014). Additionally, MRP8/14 may stimulate individual sleep-related cytokines or alter the Th1/Th2 ratio, which is associated with sleep quality. Lack of variability in the protein concentrations and in the actigraphy sleep variables between the groups and/or the use of actigraphy rather than PSG to measure sleep may explain why we did not find differences in S100A12 concentration. Recent studies in adults and children without arthritis have reported positive associations between S100A12 and MRP8/14 concentrations and sleep fragmentation (e.g., sleep-disordered breathing; Bhattacharjee et al., 2012; Kim, Bhattacharjee, et al., 2012; Kim et al., 2010; Shi et al., 2013). These studies used PSG, a more invasive sleep measure that can identify sleep disorders, and the participants had more disturbed sleep including mild and moderate to severe sleep-disordered breathing, which may explain their findings (Bhattacharjee et al., 2012; Kim, Alotaibi, Kheirandish-Gozal, Capdevila, & Gozal, 2012; Kim et al., 2010; Shi et al., 2013). Future studies should include both actigraphy and PSG to provide a better understanding of the interrelations between inflammatory biomarkers and severity of sleep fragmentation. The underlying mechanism of the associations are not well understood and require further study.

Several limitations of the present study require comment. Our sample was small, and many more of the children were diagnosed with polyarticular, as opposed to extended oligoarticular JIA. Our sample lacked variability in pain and biomarker levels, which likely contributed to our findings. The cross-sectional design limits our ability to discern directionality. Researchers designing future studies might consider obtaining serum protein samples during active disease; using PSG, a more sensitive measure of sleep fragmentation in relation to protein biomarkers; and recruiting a larger sample of children with JIA with varying types and levels of disease activity.

Clinicians and parents often overlook and/or do not recognize the problem of sleep fragmentation in children with JIA. In the few studies that have objectively measured sleep in JIA, authors have reported both sleep-disordered breathing and periodic limb movements (Passarelli et al., 2006; Ward et al., 2008, 2010; Zamir et al., 1998). In children with chronic conditions like JIA, sleep disturbances may be a sign of an unrecognized sleep disorder that manifests as sleep fragmentation. Fragmented sleep and its pathophysiological consequences may contribute to poor health outcomes in JIA and place these children at greater risk for adverse long-term effects including lower quality of life, comprised school performance, and poor disease management.

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Author Contribution

T. M. Ward, J. Voss, W. Yuwen, D. Foeel, F. Gohbar, and S. Ringold contributed to conception, design, data acquisition, data analysis, and interpretation; drafted manuscript; critically revised manuscript; and gave final approval agrees to be held accountable for all aspects of work, ensuring integrity and accuracy.

Declaration of Conflicting Interests

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