Sleep Disturbances and Neurobehavioral Performance in Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** To examine the extent of polysomnographic (PSG) sleep disturbances [obstructive apnea hypopnea index (OAHI), number of wake bouts, arousals, periodic limb movements] and the effect of OAHI on neurobehavioral performance in juvenile idiopathic arthritis (JIA) with obstructive sleep apnea (OSA), JIA without OSA, and controls without OSA, adjusting for intelligence quotient (IQ), pain, medications, daytime sleepiness, and wake bouts.

Methods. Children 6–11 years, 68 with JIA and 67 controls, underwent 1 night of PSG and completed self-reported daytime sleepiness surveys, multiple sleep latency tests for physiological sleepiness, and neurobehavioral performance tests the next day.

Results. Compared with JIA and controls without OSA, mean OAHI and arousals were significantly higher in JIA with OSA ($p < 0.001$, respectively). In comparison with JIA and controls without OSA, mean simple reaction time and sustained attention were significantly slower in JIA with OSA, adjusting for IQ, pain, any medication, daytime sleepiness, and wake bouts.

Conclusion. Elevated OAHI is suggestive of obstructive sleep apnea and a comorbidity in JIA that may predispose children with JIA to daytime sleepiness and impaired neurobehavioral performance. (J Rheumatol First Release January 15 2017; doi:10.3899/jrheum.160556)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS DAYTIME SLEEPINESS POLYSOMNOGRAPHY
OBSTRUCTIVE SLEEP APNEA NEUROBEHAVIORAL PERFORMANCE CANTAB

Sleep disturbance from obstructive sleep apnea (OSA) is a costly[1,2] serious health concern[3] associated with negative health outcomes (e.g., daytime sleepiness, lower quality of life)[4,5]. In our previous study[6] of 73 children with juvenile idiopathic arthritis (JIA), 40% had an elevated apnea/hypopnea index suggestive of OSA, and 19% of these children showed physiological daytime sleepiness on multiple sleep latency tests (MSLT). Regardless of active or inactive JIA, the apnea/hypopnea index was inversely associated with reaction time (RTI; $p < 0.001$), and the number of wake bouts (an indicator of sleep fragmentation) was inversely associated with RTI and with the probability of making a correct response ($p < 0.05$), controlling for intelligence quotient (IQ), medications, and pain[6]. These findings were the first to link physiologic objective measures of sleep disturbance with validated cognitive test results in JIA. However, we did not examine whether the associations between OSA and altered neurobehavioral function were unique to JIA, JIA and OSA, or represented similar effects in healthy children.

The objectives of our current study were to examine the extent of polysomnographic (PSG) sleep disturbances [obstructive apnea hypopnea index (OAHI), number of wake bouts, arousals, periodic limb movements] and the effect of OAHI on neurobehavioral performance in JIA with OSA, JIA without OSA, and controls without OSA, adjusting for IQ, maternal education, pain, medications, daytime sleepiness, and wake bouts. Based on our prior findings of OSA, daytime sleepiness, and altered neurobehavioral performance in JIA, we hypothesized that JIA with OSA would have increased OAHI, increased daytime sleepiness, slower movement time

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and RTI, and decreased sustained attention compared with JIA and control without OSA.

MATERIALS AND METHODS

Recruitment and screening. The Institutional Review Board approved this study (Seattle Children's IRB #13532). Written informed consent was obtained from parents; assent was obtained from children. All participants were recruited from the Seattle Children's rheumatology clinic from October 2011 through December 2014. A research coordinator screened the clinic records for potential JIA participants. Subsequently, during a routine clinic visit, the coordinator met with eligible participants to confirm eligibility, discuss the study, and invite participation. Control children were recruited from eastern and western Washington through flyers, media advertisements, and from friends and/or relatives of children with JIA. Interested families contacted a member of the team who screened participants through a telephone interview, confirmed eligibility, described the study, and invited participation. After agreeing to participate in our study, children and their parents were scheduled for an overnight sleep study.

Participants. A convenient sample of 143 children, 6–11 years, with JIA (n = 68) and controls (n = 75) participated in our study. Subjects were excluded if they had a diagnosis from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria [e.g., attention-deficit hyperactivity disorder (ADHD)], diagnosed sleep disorder (e.g., OSA) by parent report or medical record, history of adenotonsillectomy, obesity, family history of narcolepsy, and Tanner stage ≥ 3. Because of the prevalence of asthma and allergies, subjects were eligible if they had no asthma or allergy exacerbations and required no medication 1 month prior to the study [asthma, n = 8 (4 JIA); allergic rhinitis, n = 18 (6 JIA)]. Eight control children who met the clinical criteria for OSA were excluded because this group was too small to conduct analysis. The final sample consisted of 135 children (68 JIA, 67 controls).

Of the 120 JIA families screened, 52 declined to participate. Of those who declined, 53% had comorbid conditions or were too busy. Of the 140 control families, 65 declined to participate. Of those who declined, 65% had comorbid conditions, 10% had a previous adenotonsillectomy, and 25% had schedule conflicts.

General procedures. Children, accompanied by a parent, arrived at the Sleep Research Laboratory for 1 night of PSG, and on the next day completed an MSLT protocol and neurobehavioral performance tests.

Polysomnography. An overnight PSG was performed according to national standards[7,8]. Obstructive apnea was defined as cessation of airflow with ongoing thoracoabdominal effort for at least 2 respiratory cycles. Hypopnea was defined as a > 50% reduction in airflow with ongoing thoracoabdominal effort resulting in either an arousal or an oxyhemoglobin desaturation of > 3% or more. OAHI was defined as the number of obstructive apneas and hypopneas per hour of sleep. Periodic leg movements (≥ 4 leg movements, of 0.5–5 s duration with an interval of 5–90 s) and arousals (shift to a fast electroencephalography frequency lasting 3–15 s) were scored manually and expressed as an index/hour of total sleep time. Snoring time during any sleep stage was scored as an increase in the amplitude of the snore signal by > 1.5 times of a baseline line signal[6]. A wake bout was defined as an awakening of at least one 30-s epoch duration and reported as the total number of bouts that occurred throughout the sleep period. A board-certified pediatric sleep physician interpreted each study and verified OSA based on the number of OAHI ≥ 1.5[8]. OSA severity was categorized according to the OAHI: (1) mild OSA = ≥ 1.5 to < 5, (2) moderate OSA = ≥ 5 to < 10, and (3) severe OSA = ≥ 10.

Standard sleep variables were calculated. The amount of time in nonrapid eye movement (NREM) stages, rapid eye movement (REM) stage, and wake after sleep onset were expressed as percentages of sleep period time (time from sleep onset until final awakening). Total sleep time was the amount of time in NREM stages and REM. Sleep latency was the time from lights out to first epoch of NREM stage 2. Sleep efficiency was expressed as a ratio of total sleep time/time in bed.

Using the MSLT protocol. Physiological daytime sleepiness was evaluated with an MSLT protocol of 4 nap opportunities of 20-min duration conducted at 2-h intervals (9 AM, 11 AM, 1 PM, 3 PM)[9]. For each nap opportunity, a child was placed in a dark quiet room and was asked not to resist falling asleep. Sleep latency was defined as the minutes from lights out to the first epoch of NREM stage 1 sleep. Latency to sleep was reported for each nap opportunity and averaged over the 4 nap opportunities for each child.

Self-report daytime sleepiness. Child-report of daytime sleepiness was assessed before and after each nap opportunity. Children completed a visual analog scale and placed an "X" on the line (100 mm) to express how sleepy s/he felt at the time ("extremely awake" face, "extremely sleepy" face). Results were reported in millimeters from the "extremely awake" end of the scale. Children < 8 years were assisted by the laboratory staff to complete this scale.

Wechsler Abbreviated Scale of Intelligence (WASI). In the afternoon, between 2 MSLT, a neuropsychologist administered the WASI, a test of cognitive ability that includes 3 dimensions of intelligence (verbal, performance, and full IQ), standardized for age and sex (Pearson).

Cambridge Neuropsychological Test Automated Battery (CANTAB). Children completed computer-based neurobehavioral performance tests (CANTAB; Cambridge Cognition)[10]. The test battery was administered upon arrival to the sleep laboratory as a practice session, and the following morning at 10 AM as a test session.

CANTAB test domains included (1) a motor screening test, a measure of movement time; (2) RTI, a measure of visual scanning and processing speed with 2 tests (simple and 5-choice); (3) match to sample visual search (MTS) tests, a measure of recall and RTI that involved a visual search strategy to accurately identify a specific object; and (4) rapid visual processing (RVP), a measure of sustained attention. CANTAB scores for each test are standardized for age and sex, and were averaged over the trials for each test.

RTI was used to measure the time it takes to touch the target after the press pad has been released with 1-choice (simple) and 5-choice stimulus conditions. MTS test was used to evaluate speed and visual recognition to recall patterns. MTS variables included (1) MTS percent correct, the number of correctly identified responses out of a possible 48 presented and reported as the proportion of correct responses; and (2) MTS latency to change 2–8, the time needed to correctly identify a target presented from 2 choices versus 8 choices. RVP was a measure of sustained visual attention (e.g., how good the participant was at detecting the target sequences). RVP variables included (1) the probability to a hit, the proportion of correct responses when a target sequence was presented; and (2) the probability of false alarm, the proportion of responses when no target sequence was presented (e.g., inappropriate responses).

Demographic and clinical characteristics. Parents completed questionnaires about their child's age, ethnicity, and the highest level of maternal education. Children reported pain intensity and number of joints that hurt in the evening prior to the sleep study. Pain intensity was measured with the Oucher Faces Rating pain scale (0 = no hurt, 10 = the biggest hurt)[11]. Number of joints that hurt was measured by a skeleton figure where children circled the joints that corresponded to location of the pain[12].

JIA disease duration was measured from the date the child was first diagnosed. Prior to the scheduled sleep study, a pediatric rheumatologist confirmed JIA subtype and disease activity according to (1) the physician's global assessment (PGA) on a scale of "0 = no disease" to "10 = very severe disease"; and (2) the number of active joints, defined as the number of joints with active synovitis during the examination. Active disease was defined as synovitis of 1 or more joints, along with active uveitis, and PGA > 0; inactive disease was defined as no active joints, joint synovitis, or uveitis, and a PGA = 0[13].

Medications. Parents recorded medications their child received during the study as "yes" or "no" and classified as (1) disease-modifying antirheumatic drugs (methotrexate), (2) sulfasalazine, (3) biologics (e.g., etanercept), (4) nonsteroidal antiinflammatory drugs, (5) glucocorticoids, (6) other (vitamin D, zinc, multivitamins), and (7) none.

Statistical analysis. Data were analyzed using SPSS for Windows version 17.0 (SPSS Inc.) and Stata version 14.1 (StataCorp LP). Preliminary analyses showed no differences in PSG sleep, sleep disturbances (OAHI, wake bouts, arousals, periodic limb movements), daytime sleepiness (self-report, MSLT nap opportunities), and CANTAB test domains (movement time, RTI, sustained attention) based on active and inactive JIA; therefore, disease activity was not included in any subsequent analysis.

The first analyses tested group differences on demographics and clinical characteristics. Statistical comparison tests between the groups were performed using Student t tests for normally distributed continuous variables, and the chi-square and Fisher's exact tests for categorical variables. Because 51% of children with JIA (n = 35) had an OAHI ≥ 1.5, the second set of analysis tested differences among JIA with OSA (n = 35), JIA without OSA (n = 33), and controls without OSA (n = 67) on PSG sleep, sleep disturbances, neurobehavioral performance scores, and daytime sleepiness. Statistical comparison tests between the groups were performed using ANOVA for normally distributed continuous variables, chi-square tests for categorical variables, and Kruskal-Wallis tests for non-normally distributed variables.

The third analyses examined the effect of OAHI on neurobehavioral performance scores across 3 groups (JIA with OSA, JIA without OSA, and controls without OSA). A series of regression models analyzed neurobehavioral performance by group (e.g., unadjusted models). Subsequently, we examined the effect of group adjusting for covariates including IQ, maternal education, pain, medications, sleep latency for the first nap opportunity, and number of wake bouts (e.g., adjusted models). The sleep latency for the first nap opportunity was used in the regression models because sleepiness fluctuates across a day, and this nap opportunity was the most proximal to the time the neurobehavioral tests were administered to provide the best control for sleepiness.

RESULTS

Demographic and clinical characteristics. Table 1 shows the demographics among the 3 groups; significant group differences were found for maternal education. In comparison with the mothers of patients with JIA with and without OSA, mothers of control group children were more highly educated (Fisher's exact test, $p < 0.01$). Table 2 shows the clinical characteristics between JIA children with OSA and JIA without OSA; no significant differences were found.

PSG sleep, sleep disturbances, and daytime sleepiness. Table 3 shows data for PSG sleep, sleep disturbances, and daytime sleepiness for JIA with OSA, JIA without OSA, and controls without OSA. ANOVA revealed significant differences among the 3 groups for OAHI (chi-square = 76.8, $p < 0.001$) and arousals [$F_{(2,134)} = 8.0$, $p < 0.001$]. Posthoc comparisons showed significantly higher OAHI and arousals in JIA with OSA compared with JIA and controls without OSA ($p < 0.001$). Of the JIA children with OSA, 47% had mild to moderate OSA and 4.4% had severe OSA. Self-report sleepiness and the mean of the 4 nap opportunities did not significantly differ among the groups.

Table 1. Demographics. Values are mean ± SD or n (%).

Characteristics	JIA with OSA, n = 35	JIA without OSA, n = 33	Control, n = 67	p
Age, yrs	8.7 ± 1.8	8.4 ± 1.9	8.8 ± 1.6	0.52
Child's ethnicity				0.57
White	23 (65.7)	25 (75.8)	46 (68.7)	
Mixed race	7 (20.0)	4 (12.1)	10 (14.9)	
Girls	20 (57.1)	18 (54.5)	40 (59.7)	0.88
Maternal education				0.01
High school	3 (8.6)	1 (3.0)	7 (10.4)	
Some college, 1–3 yrs	14 (40.0)	16 (48.5)	9 (13.4)	
College degree	10 (28.6)	8 (24.2)	25 (37.3)	
Master's degree or higher	8 (22.9)	8 (24.2)	25 (37.3)	

JIA: juvenile idiopathic arthritis; OSA: obstructive sleep apnea.

Table 2. Clinical characteristics. Values are mean ± SD or n (%).

Characteristics	JIA with OSA, n = 35	JIA without OSA, n = 33	p
Disease subtype			0.15
Oligoarticular	6 (17.1)	13 (39.4)	
Extended oligoarticular	7 (20.0)	6 (18.2)	
Polyarticular RF–negative	12 (34.3)	10 (30.3)	
Polyarticular RF–positive	0 (0)	1 (3.0)	
Systemic	6 (17.1)	1 (3.0)	
Enthesitis-related	2 (5.7)	2 (6.1)	
Psoriatic	2 (5.7)	0 (0)	
JIA disease activity			0.30
Active	16 (45.7)	11 (33.3)	
Inactive	19 (54.3)	22 (66.7)	
Physician's global rating, 0–10	1.03 ± 1.5	0.75 ± 1.5	0.76
Disease duration, mos	38.8 ± 28.7	36.6 ± 28.8	0.75
Active joint count	1.74 ± 3.8	1.4 + 5.3	0.91
Pain			
Evening pain	0.86 ± 1.4	0.55 ± 1.3	0.15
Evening joint count			0.51
0	25 (71.4)	27 (81.8)	
1	5 (14.3)	4 (12.1)	
2	3 (8.6)	2 (6)	
3	2 (5.7)	0 (0)	
Medications			
DMARD	14 (40.0)	18 (54.5)	
Sulfasalazine	4 (11.4)	1 (3.0)	
Biologics	10 (28.6)	6 (18.2)	
NSAID	16 (45.7)	11 (33.3)	
Corticosteroids	1 (2.9)	2 (6.1)	
Other, vitamins	19 (54.3)	20 (60.6)	
No medication	4 (11.4)	6 (18.2)	

JIA: juvenile idiopathic arthritis; OSA: obstructive sleep apnea; RF: rheumatoid factor; DMARD: disease-modifying antirheumatic drugs; NSAID: nonsteroidal antiinflammatory drugs.

WASI and neurobehavioral performance. Table 4 shows the mean scores for the WASI and the CANTAB variables with maternal education as a covariate. Adjusting for multiple comparisons ($p < 0.006$), ANOVA revealed no significant differences for verbal, performance, and total IQ scores, or for any of the CANTAB variables among the 3 groups (Table 4).

Bivariate correlations. Bivariate correlations showed that OAHI was positively associated with pain ($r = 0.20$, $p < 0.02$) and any medication ($r = 0.25$, $p < 0.002$). Number of wake bouts was positively associated with total IQ ($r = 0.26$, $p < 0.002$) and RVP probability to hit a correct target sequence ($r = 0.27$, $p < 0.002$). Total IQ was positively associated with maternal education ($r = 0.41$, $p < 0.001$) and MTS percent

Table 3. PSG sleep, sleep disturbances, and daytime sleepiness. Values are mean ± SD. Bonferroni correction for multiple comparisons with p < 0.002.

Variables	JIA with OSA, n = 35	JIA without OSA, n = 33	Controls without OSA, n = 67	p[b]
PSG sleep variables				
Time in bed, min	583.6 ± 33	567.1 ± 42	567.6 ± 33	0.07
TST, min	498.4 ± 65	491.3 ± 69	475.6 ± 58	0.18
Sleep efficiency, %	85.4 ± 10	86.7 ± 11	83.8 ± 9	0.38
Sleep latency stage 2, min	32.5 ± 30	37.8 ± 32	38.0 ± 35	0.71
Wake after sleep onset, % SPT	9.1 ± 9.3	8.0 ± 8.8	9.4 ± 7.6	0.74
NREM, stages 1, 2, 3, % SPT	72.2 ± 7	73.5 ± 8	72.2 ± 6	0.78
REM, % SPT	18.7 ± 4	19.3 ± 5	17.1 ± 5	0.26
Mean oxygen saturation, %	97.5 ± 0.61	97.7 ± 0.51	97.6 ± 0.59	0.23
PSG sleep disturbances				
Snoring, min	287.3 ± 127	216.4 ± 118	251.1 ± 123	0.06
Arousals/h TST	10.3 ± 2.8	7.7 ± 2.4	8.8 ± 2.7	< 0.001
Wake bouts	19.0 ± 8.4	19.2 + 8.2	19.8 ± 7.5	0.86
OAHI/h TST	4.7 ± 4.8	0.86 ± .38	0.99 ± 0.41	< 0.001
Periodic limb movement/h TST	2.3 ± 6.1	1.6 ± 2.9	1.6 ± 3.3	0.68
Daytime sleepiness				
Self-report sleepiness, min	5.3 ± 4.4	5.5 ± 4.7	6.2 ± 5.2	0.73
Average MSLT sleep latency, min[a]	15.3 ± 4.6	15.6 ± 4	17.4 ± 3.6	0.03
MSLT # 1, min	16.3 ± 5	16.9 ± 5	18.4 ± 4	0.07
MSLT # 2, min	15.5 ± 6	17.3 ± 4	18.1 ± 4	0.04
MSLT # 3, min	14.2 ± 7	14.7 ± 6	16.3 ± 5	0.19
MSLT # 4, min	15.0 ± 6	13.7 ± 6	16.6 ± 5	0.06

[a] Average MSLT sleep latency are mean of 4 nap opportunities and SD. [b] One-way ANOVA used for normally distributed variables; Kruskal-Wallis tests used for AHI and periodic limb movement. PSG: polysomnographic; JIA: juvenile idiopathic arthritis; OSA: obstructive sleep apnea; TST: total sleep time; SPT: sleep period time; NREM: nonrapid eye movement; REM: rapid eye movement; OAHI: obstructive apnea hypopnea index; MSLT: multiple sleep latency test.

Table 4. WASI and neurobehavioral performance. Values are mean ± SD. Bonferroni correction for multiple comparisons with p < 0.006.

Variables	JIA OSA, n = 35	JIA without OSA, n = 33	Controls without OSA, n = 67	p
WASI				
Verbal	113.1 ± 14	106.9 ± 16	113.7 ± 16	0.30
Performance	105.6 ± 13	100.6 ± 12	110.2 ± 16	0.03
Full score	110.4 ± 12	103.9 ± 13	113.5 ± 15	0.06
CANTAB variables				
RTI simple, ms	436.5 ± 105	436.4 ± 133	385.8 ± 98	0.03
RTI 5-choice, ms	454.1 ± 94	439.3 ± 93	416.0 ± 105	0.20
MTS percent correct, %	94.3 ± 7	96.8 ± 6	94.5 ± 7	0.26
MTS mean latency change, 2–8, ms	2040.9 ± 1350	2769.6 ± 1733	2113.9 ± 1533	0.07
RVP probability to hit, pr	0.28 ± 0.19	0.34 ± 0.21	0.40 ± 0.23	0.08
RVP probability of false alarm, pr	0.03 ± 0.05	0.03 ± 0.06	0.02 ± 0.03	0.32

Maternal education included as a covariate for all outcomes. Raw CANTAB scores. WASI: Wechsler Abbreviated Scale of Intelligence; CANTAB: Cambridge Neuropsychological Test Automated Battery; RTI: reaction time test; MTS: match to sample test; RVP: rapid visual information processing test; pr: probability range 0–1.

correct (r = 0.19, p < 0.03), and was negatively associated with any medication (r = –0.21, p < 0.02) and RVP probability to hit false alarm (r = –0.25, p < 0.004). Pain was positively associated with any medication (r = 0.33, p < 0.001) and negatively associated with maternal education (r = –0.18, p < 0.05). Based on the bivariate correlations, these were adjusted for in each of the regression models: IQ, maternal education, pain, medication, and the number of wake bouts.

OSA and neurobehavioral performance. Among the CANTAB tests, RVP probability to hit and simple RTI were statistically significant among the groups. For RVP probability to hit scores, the effect of group was significant [$F_{(2,120)}$ = 3.9, p < 0.02], such that JIA with OSA had a decreased probability of hitting the correct target sequence in comparison with controls without OSA (Table 5), but RVP probability to hit scores were not significantly different between JIA with and without OSA (t = –1.0, p = 0.31). In the adjusted model for RVP probability of hit, the effect of group remained significant [$F_{(2,112)}$ = 3.4, p < 0.04]. In comparison with controls, JIA with OSA had a significantly lower probability to hit the correct target sequence (t = –2.5,

Table 5. OSA and neurobehavioral performance.

Variables	β	95% CI	β	p	Adjusted R^2
RVP probability to hit					
Step 1 – Group[a]					0.05
JIA with OSA	–0.13	–0.22 to –0.03	–0.26	0.007	
JIA without OSA	–0.07	–0.17 to 0.02	–0.14	0.15	
Step 2 – Group + covariates					0.17
JIA with OSA	–0.17	–0.30 to –0.03	–0.34	0.01	
JIA without OSA	–0.07	–0.20 to 0.05	–0.15	0.25	
IQ	0.00	–0.00 to 0.01	0.17	0.08	
Maternal education[b]					
High school	–0.04	–0.22 to –0.15	–0.04	0.69	
Some college, 1–3 yrs	–0.07	–0.17 to 0.03	–0.15	0.16	
College degree	–0.00	–0.10 to 0.10	–0.00	0.98	
Pain	0.02	–0.02 to 0.07	0.09	0.30	
Any medication	0.04	–0.08 to 0.16	0.09	0.48	
MSLT	–0.01	–0.02 to –0.00	–0.26	0.003	
Wake bouts	0.00	–0.00 to –0.01	0.17	0.03	
RTI mean, simple					
Step 1 – Group[a]					0.04
JIA with OSA	54.96	10.39–99.52	0.23	0.02	
JIA without OSA	46.15	–0.24 to 92.53	0.19	0.05	
Step 2 – Group + covariates					0.07
JIA with OSA	97.3	30.4–164.2	0.41	0.005	
JIA without OSA	82.5	16.7–148.3	0.34	0.01	
IQ	0.30	–1.2 to 1.8	0.04	0.70	
Maternal education[b]					
High school	38.5	–56.3 to 133.2	0.08	0.42	
Some college, 1–3 yrs	12.7	–39.0 to 64.3	0.06	0.63	
College degree	–33.1	–80.9 to 14.7	–0.15	0.17	
Pain	–10.5	–32.4 to 11.4	–0.09	0.34	
Any medication	–38.3	–97.9 to 21.3	–0.18	0.21	
MSLT	5.1	1.1–9.1	0.23	0.01	
Wake bouts	–0.3	–2.8 to 2.1	–0.03	0.79	

[a] Controls without OSA (reference group). [b] Master's degree or higher (reference group). OSA: obstructive sleep apnea; RVP: rapid visual information processing test; JIA: juvenile idiopathic arthritis; IQ: intelligence quotient; MSLT: multiple sleep latency test; RTI: reaction time test.

$p < 0.01$). RVP probability to hit was similar between JIA with and without OSA, after adjusting for the covariates.

For RTI simple RTI, the effect of group was significant [$F_{(2,118)} = 3.7$, $p < 0.03$], such that JIA with OSA had significantly longer RTI than controls without OSA ($t = 2.4$, $p < 0.02$; Table 5). Simple RTI was also longer in JIA without OSA than in controls without OSA ($t = 1.97$, $p = 0.051$). No significant differences in RTI were found between JIA with and without OSA. In the adjusted model, the effect of group remained significant [$F_{(2,110)} = 4.4$, $p < 0.02$], adjusting for the covariates. In comparison with controls without OSA, simple RTI was significantly longer in JIA with and without OSA ($t = 2.9$, $p < 0.005$ and $t = 2.5$, $p < 0.02$, respectively). However, simple RTI did not differ between JIA with and without OSA, adjusting for covariates ($t = –0.56$, $p = 0.58$).

DISCUSSION

In JIA, an elevated OAHI was common. In comparison with controls, our findings suggest that measures of neurobehavioral performance that are considered sensitive to disturbed sleep (e.g., simple RTI, sustained visual attention) were impaired in JIA with OSA.

Neurobehavioral performance. We found a significant group effect for sustained visual attention and simple RTI in the JIA with OSA. The probability to hit a correct target, a measure of sustained visual attention, was lower in JIA with OSA than controls. Mild to moderate OSA may lead to more lapses in attention with a tendency to incorrectly respond to the correct target sequence.

Prior studies in children with OSA have reported positive associations between OAHI and poor sustained attention using different neuropsychological assessments than those used in our study[14,15,16]. However, the findings from these studies are mixed with respect to OSA severity and neurobehavioral performance[17,18,19,20,21]. For example, Karpinski, *et al* reported positive associations between OSA severity and a working memory deficit, but Giordani, *et al* found that children with less severe OSA performed significantly worse on measures of working memory. It is possible that different

types of neurobehavioral tests used in these studies would account for these inconsistent findings.

We found a significant group effect for simple RTI. In comparison with controls without OSA, both JIA groups with and without OSA had significantly slower simple RTI. This finding suggests that JIA disease, rather than OSA comorbidity alone, could affect how quickly a child responds to stimuli. Although disease activity and pain levels were low, the underlying disease inflammation, physical function, and/or dexterity in the hands and wrists may contribute to this finding. JIA with OSA had slower RTI, but the scores were not significantly different from JIA without OSA and controls. We anticipated that a breathing abnormality during sleep could be related to difficulty in responding to multiple stimuli (e.g., making slower responses), but this was not observed. Nevertheless, our finding of slower simple RTI is similar to previous studies in children with OSA that showed negative associations between OSA and tests of speed and accuracy[5,14,15,16,22]. We had anticipated finding significant differences in sustained visual attention and simple RTI between JIA with and without OSA, but this was not observed. Few studies have examined OSA in JIA with PSG[23], and the effect of OSA on neurobehavioral performance remains poorly studied. Longitudinal studies are needed to examine the trajectories in neurobehavioral performance as a function of OSA, which would provide new knowledge about the clinical implications of OSA in these children.

Daytime sleepiness. Self-reported sleepiness and average sleep latency for the nap opportunities in the JIA groups were similar to those reported previously[6]. Contrary to our hypothesis, the nap opportunities were not significantly different among the groups. This observation was not attributed to the high proportion of OSA or other sleep measures. This finding may be explained by a change in children's daily routine during our study. For example, children remained in the sleep laboratory for several hours after the overnight sleep study, and this alteration in daily routine may have induced daytime sleepiness (e.g., boredom) for some children. Regardless of the etiology, in comparison with studies of healthy controls[24,25,26,27] that report average MSLT sleep latency of 27.5 min, children in our study had much shorter latencies, suggestive of some degree of daytime sleepiness. Daytime sleepiness is a common symptom of OSA[28,29,30] and is present in JIA[6,25]; it may place children at risk for poor school performance or attention problems. Daytime sleepiness is an important covariate to include in studies of OSA and neurobehavioral performance.

In JIA, an elevated OAHI, suggestive of OSA, is important for several reasons. First, the symptoms of OSA in JIA are not routinely assessed in clinical practice. Sleep disturbances are often attributed to pain, JIA-related fatigue, and/or medication side effects, without adequately screening for treatable underlying sleep disorders such as OSA. Second, daytime sleepiness is a common symptom of OSA, and studies of otherwise healthy children who are sleepy during the day have shown them to be at high risk for inattention or impulsivity, which can lead to misdiagnosis of ADHD[31]. Third, the average time from JIA diagnosis to the identification of OSA by PSG was 2½ years (data not shown), implying that some children could have been experiencing OSA for several years. Timely diagnosis and treatment is important because children with JIA may be more vulnerable to the consequences of OSA. OSA may also complicate clinical management and important health outcomes.

The high prevalence of OSA may be related to temporomandibular joint involvement and retrognathia, both common in JIA and risk factors for OSA[23]. Currently, to our knowledge, there are no screening or treatment guidelines for OSA in JIA. The Pediatric Sleep Questionnaire (PSQ), a validated 1-page, sleep-related breathing symptom survey[32], with a clinical OSA cutoff score, may be a useful screening measure. Studies in control children show that the PSQ is positively associated with OAHI, and predicts improvements in key clinical outcomes including behavior, quality of life, and sleepiness before and after adenotonsillectomy[20,33]. To date, there have been no longitudinal sleep studies using PSG that examine the OSA in JIA, and whether OSA treatment (adenotonsillectomy) resolves OSA and changes in neurobehavioral function. Longitudinal studies would provide knowledge about the effect of OSA treatment on neurobehavioral function and disease-related symptoms, which would increase awareness among pediatric providers and pediatric rheumatologists of the need for systematic and routine screening for OSA.

Limitations. There are study limitations that deserve comment. First, PSG was obtained for 1 night. Although this is consistent with clinical practice, and enabled comparisons to previous studies, a single night may not fully characterize typical sleep. Second, medications were included as a covariate in the regression analysis because we had too few children taking each type of medication to conduct a more refined analysis. To our knowledge, the cognitive effects of medication in JIA are not well characterized. Third, although our control and JIA groups were not matched on maternal education, they fit closely on other demographic factors and we controlled for maternal education in the analyses. Last, physical function and dexterity were not measured and may contribute to the neurobehavioral test scores. However, elevated OAHI in JIA and altered neurobehavioral performance function are consistent with our prior work and support reproducibility of the findings.

OSA was prevalent in JIA and may predispose children to daytime sleepiness and impaired neurobehavioral performance. Effective detection and treatment of OSA may reduce morbidity, decrease healthcare costs, and improve disease management.

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