Correlates of Sleep and Pediatric Bipolar Disorder

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Study Objective: To determine, based on a large community sample, the prevalence and associated sleep characteristics of children with a bipolar mood disturbance behavioral profile.

Methods: Participants who fit the pediatric bipolar disorder profile as derived from the Child Behavior Checklist were matched to control participants for age, sex, ethnicity, parentally reported attention-deficit/hyperactivity disorder, psychotropic medication usage, and apnea-hypopnea indexes. Paired comparisons were made between the groups to examine differences on polysomnographic data and parentally reported sleep characteristics.

Results: Thirteen (~3%) of 438 participants fit the pediatric bipolar disorder profile. These children demonstrated significant sleep-continuity disturbances with poorer sleep efficiency and more awakenings after sleep onset, less rapid eye movement sleep, and longer periods of slow-wave sleep than their matched counterparts during overnight polysomnography. In addition, responses to a parental-report questionnaire about child sleep behavior suggest these children have significant sleep problems, including more difficulty initiating sleep, restless sleep, nightmares, and morning headaches relative to the control group.

Conclusions: Children with a pediatric bipolar disorder profile display consistent quantitative differences in sleep relative to matched controls. Prevalence rates of pediatric bipolar disorder profile display consistent quantitative differences in sleep relative to matched controls. Prevalence rates of pediatric bipolar disorder profile display consistent quantitative differences in sleep relative to matched controls. Prevalence rates of pediatric bipolar disorder profile display consistent quantitative differences in sleep relative to matched controls.

INTRODUCTION

SLEEP DISTURBANCE HAS BEEN INCORPORATED AS AN INCLUSION CRITERION OF AFFECTIVE DISORDER AND IS CLEARLY A DEFINING FEATURE OF BIPOLAR depression.1 However, current understanding of the relationship between mood and sleep remains quite limited, particularly in the pediatric population.2 In the present study we examine the prevalence and associated sleep characteristics of children with a bipolar mood disturbance behavioral profile.

The predominant features of pediatric bipolar disorder (PBD) are elation, grandiosity, flight of ideas or racing thoughts, decreased need for sleep, and hypersexuality during manic states.3,4 The disorder has also been characterized by severe irritability and high levels of hyperactivity.5 Although the presence of mania in the pediatric population has been reported in earlier work,6 more recent evidence suggests that, unlike mania in adults, it is characterized by nonepisodic, chronic, mixed states of ultra rapid cycling or “ultradian” cycling (as many as 300 manic episodes per year or more) with severe irritability.7 Although some controversy remains in the literature regarding the diagnostic validity of PBD, there is increasing evidence supporting its legitimacy as a distinct diagnostic entity. Indeed, consistent with established guidelines,8 uniquely differentiating features, evidence of familiality, specific treatment responsivity, and unique course of the disorder have been identified.9,12 In fact, a National Institute of Mental Health (NIMH) roundtable discussion resulted in the statement that PBD is a valid diagnostic entity and can be diagnosed accurately in prepubertal children13 despite the complexity of symptomatology, differences in adult versus childhood presentation, degree of symptom overlap with other mental disorders, and even in the presence of developmentally appropriate behavior.

Two studies have identified sleep characteristics associated with PBD. Rao et al14 used long-term clinical course to separate adolescents who were depressed at the time the sleep study was conducted into those who eventually developed bipolar disorder and those who continued to have unipolar depression. The bipolar group evidenced significantly more Stage 1 sleep than healthy controls. Both the bipolar group and the healthy controls had increased rapid eye movement (REM) latency, lower REM density, and less REM sleep than the unipolar group. Decreased need for sleep is a diagnostic criterion for PBD.1 Consistent with this criterion, Geller et al15 reported that 40% of children with mania, but only 6.2% of children with attention-deficit/hyperactivity disorder (ADHD) and 1.1% of community controls, presented with dramatically decreased need for sleep.

Diagnostic uncertainty for PBD is compounded by high comorbidity with ADHD and to a lesser extent with conduct and anxiety disorders.4 These factors, along with the lack of epidemiologic research, lead to a relative paucity of information regarding the prevalence and age of onset for PBD.15 Studies have shown that approximately 7% of children seen at psychiatric facilities meet criteria for PBD.12 Furthermore, Strober16 found that as many as 20% of children diagnosed with unipolar depression went on to develop PBD later in life. Adult epidemiologic data from a recent large community sample of 127,000 people estimated the prevalence of bipolar disease between 3.4% and 3.7% using a mood disorder screening questionnaire, with only 1.4% reporting a formal diagnosis, a finding that is consistent with other studies.17 Evidence from a relatively small cohort of bipolar children examined by Biederman and colleagues8 suggested early onset (6.3 ± 4.7 years) for PBD, and NIMH guidelines further suggest

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that a valid assessment of PBD can be made as early as 4 years of age.\textsuperscript{13}

As further evidence of the critical importance of this issue, particularly as it refers to the devastating impact to the individual as well as the healthcare community, the NIMH has recently assigned a high priority to the advancement of knowledge in this area.\textsuperscript{13} A roundtable discussion by NIMH for the investigation of PBD\textsuperscript{21} recommended the inclusion of the Child Behavior Checklist (CBCL; see reference 19) in the investigation of PBD for the advancement of knowledge in this area. Two studies investigating the utility of the CBCL for this purpose have been conducted. Kahana et al\textsuperscript{22} used single syndrome scale T scores to try to determine cutoff values for discriminating PBD from disruptive behavior disorders, major depressive disorders, and ADHD. This approach was unsuccessful; when sensitivity was adequate, specificity was low, making discrimination of the groups impossible. When specificity was adequate, sensitivity was low. Mick et al\textsuperscript{21} took a different approach. Using random-effects meta-analysis regression,\textsuperscript{22} and taking into consideration publication bias using the method of Egger et al, Mick et al identified a 3-point elevation profile on the CBCL that characterized children with PBD. The following structured interviews were used to diagnose children in the 7 studies comprising the meta-analysis; Schedule of Affective Disorders and Schizophrenia for School-Age Children-Epidemiological Version (KSADS-E), Washington University at St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U KSADS), Diagnostic Interview for Children and Adolescents (DICA-R), and the Child Symptom Inventory-Revised (CSI-R). The point estimates (or combined predicted scores) from the random-effects meta-analysis indicated that children with bipolar disorder had T scores above 70 on the Anxious/Depressed, Attention-Hyperactivity Problems, and Aggressive Behavior syndrome scales. This 3-point elevation profile successfully differentiated patients with PBD from those with ADHD and from controls without psychiatric diagnoses. This PBD profile has shown promise as a useful aid in the clinical recognition and differential diagnosis of the disorder.\textsuperscript{21}

In the current study, we used Mick et al’s PBD profile for 2 purposes. First, we examined the prevalence in a large community sample of children who fit this profile. Second, to determine if the children who fit the PBD profile exhibited alterations in their sleep characteristics, we compared polysomnography (PSG) findings and results of a parent-report questionnaire on child sleep characteristics for the group of children with a PBD profile to those for a well-matched group of controls.

METHODOLOGY

Participants

Data from participants recruited in the first 2 years (2000-2002) from a large ongoing, National Institutes of Health-funded, community study of sleep and neurobehavioral function in 5- to 7-year-old children were used. Data from participants in the current study may be included in other publications emanating from the larger project.\textsuperscript{24-25} Parents of all children enrolled in the first grade of the Jefferson County Public School system (Louisville, KY) were invited to participate in this study, which received approval from the University of Louisville Institutional Review Board. Parental informed consent and child assent, in the presence of a parent, were obtained.

Sleep Questionnaire

A detailed sleep questionnaire probing sleep behavior, including snoring, potential indicators for daytime hypersomnolence, restless sleep, nightmares, and enuresis, was completed by the parents.\textsuperscript{24-25} Questions probing potential attention problems and hyperactivity in the child were included, and parents were directly asked if they believed their child has ADHD. The questionnaire was also used as the primary measure to screen for exclusionary criteria and included questions about the child’s general medical condition. The questionnaire is similar to one previously employed by Carroll et al\textsuperscript{26} and has been used with early elementary-aged school children\textsuperscript{27-28} and has been recently validated at our center.\textsuperscript{29} The questionnaire was modified to assign numerical scores to each of the answers ranging from 0 (never), 1 (rarely), 2 (occasionally), 3 (frequently) to 4 (almost always).

PSG Assessment

An overnight PSG assessment was performed in the sleep laboratory at Kosair Children’s Hospital, Louisville, KY. No sedation was used to induce sleep, and to alleviate separation anxiety, the parent slept in the same room as the child in a bed nearby. All children were in bed with the lights out at 9:30 PM. The following parameters were measured: chest and abdominal wall movement, heart rate, air flow and end-tidal carbon dioxide levels, arterial oxygen saturation (SpO$_2$), bilateral electrooculogram, 8 channels of electroencephalogram, chin and anterior tibial electromyograms, body position; and tracheal sound. All measurements were digitized using a commercially available PSG system (REMbrandt Systems, Medcare Diagnostics, Amsterdam, The Netherlands), and a digital time-synchronized video recording was made. Analysis of the PSG was performed using standard techniques. Sleep staging was assessed using Rechtschaffen and Kales\textsuperscript{30} criteria. The obstructive apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of total sleep time (TST), and obstructive apnea was defined as the absence of airflow with continued chest wall and abdominal movement for the duration of at least 2 breaths.\textsuperscript{31} Hypopneas were defined as a decrease in air flow of at least 50% with a corresponding decrease in SpO$_2$, of at least 4%, an arousal, or both.\textsuperscript{31} Mean SpO$_2$ and SpO$_2$ nadir were determined. Arousals were defined as recommended by the American Sleep Disorders Association Task Force report\textsuperscript{32} and included respiratory-related (occurring immediately following an apnea, hypopnea, or snore), technician-induced, and spontaneous arousals. Arousals were expressed as the total number of arousals per hour of sleep time (arousal index). Sleep efficiency was calculated as the percentage of time spent in sleep between sleep onset and termination. The majority of children were allowed to wake for the day spontaneously. The few children who did not wake by 6:45 AM were awoken at that time if they were in non-rapid eye movement (REM) sleep. Those children in REM sleep were allowed to complete the REM phase prior to awakening.

Child Behavior Checklist-Revised

The CBCL\textsuperscript{19} is one of the most popular and empirically validated parent-report checklists available.\textsuperscript{19,33} The 4- to 18-year version used for this investigation includes 8 empirically derived syndrome scales (Withdrawn, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention-Hyper-
activity Problems, Delinquent Behavior, Aggressive Behavior), 2 partial summary scales (Internalizing Problems: a combination of Withdrawn, Somatic Complaints, and Anxious/Depressed; and Externalizing Problems: a combination of Delinquent Behavior and Aggressive Behavior), and a Total Problems scale. Test-retest reliability and internal consistency estimates are in the very good to excellent range.\textsuperscript{16} The CBCL yields T scores with a mean of 50 and a standard deviation of 10 for Internalizing Problems, Externalizing Problems, and Total Problems, and each of the syndrome scales. The parent-report version of the checklist, which has been shown to be better than the teacher version as a predictor of diagnostic classification,\textsuperscript{31} was used for this study. Participants who fit Mick et al.’s 3-point elevation profile (T>70 for the Anxious/Depressed, Attention-Hyperactivity Problems, and Aggressive Behavior syndrome scales) were placed in the PBD profile group.

Data Analysis

Data are presented as mean ± SD unless stated otherwise. The PBD profile group (n=13) was compared with a control group (n=13) individually matched for age, sex, ethnicity, parentally reported ADHD, psychotropic medication usage, and AHI, using pairwise comparisons.

Paired-sample analyses were conducted using parametric t tests for the PSG data and nonparametric Wilcoxon signed ranks tests for the Likert-scaled items (sleep questionnaire). For all statistical analyses, a p value of < .05 was the criterion for statistical significance.

RESULTS

Of the 22,844 questionnaires mailed, 2,396 completed questionnaires were received or completed by telephone contact. Contact was then made with all families that did not meet exclusionary criteria (chronic medical conditions, craniofacial or genetic abnormalities, and history of tonsillectomy or adenoidectomy). A total of 438 families agreed to participate in a standard overnight multichannel PSG evaluation and subsequent neurocognitive testing at the Sleep Medicine Center of Kosair Children’s Hospital. There were no significant differences in demographic information for those families who agreed to participate and those who declined. Ethnic distribution for the sample and median income estimated by zip code using the most recent census information were comparable with the community at large and are presented in Table 1.

Thirteen (7 boys, 6 girls) of the 438 participants (2.97%) fit Mick et al.’s\textsuperscript{21} PBD profile. Parents of 8 children in the PBD profile group identified their child as White non-Hispanic, 3 as African American, 1 as “other” ethnic category, and 1 parent declined to answer. Five of the 13 children were reported by their parents to have been diagnosed with ADHD. These 5 children were matched with 4 children in the comparison group with parentally reported ADHD and to 1 child whose parent was unsure if her child met criteria for an ADHD diagnosis. Figure 1 represents a diagram of participant recruitment and selection.

Three children in the PBD profile group were reported to receive pharmacologic therapy for ADHD. Two of the 3 were reportedly taking psychostimulants amphetamine or dextroamphetamine; the third was reported to be taking an atypical antipsychotic agent (olanzapine). Two of these 3 children were also reported to receive guanfacine (antihypertensive) which, similar to clonidine hydrochloride, has been used off-label in children in conjunction with stimulants as a sleep aid and to manage stimulant-induced motor tics. These 3 children were matched, respectively, with 2 children who were also taking psychostimulants amphetamine or dextroamphetamine and 1 taking an atypical antipsychotic agent (risperidone) as well as clonidine hydrochloride (antihypertensive). Twelve of the 13 participants in the PBD profile group had an AHI less than 5 per hour of TST and no evidence for clinically relevant sleep-disordered breathing (SDB); the remaining participant had SDB (AHI: 8.8 per hour TST). Controls (n=13) were matched individually as closely as possible. The largest individual AHI difference was .32, and the mean individual difference was .08. Mean demographic, AHI, and CBCL scores for the subscales of interest are presented in Table 2. It was not possible to match 1 female pair on ethnicity. Instead, 1 girl in the risk group classified as an “other” ethnic minority was matched with an African American girl. The results were equivalent whether data from this pair were retained or excluded from the analysis.

Results of the PSG analyses are presented in Table 3 and indicate significant differences for the PBD profile group with less-efficient sleep (t=-2.56, p < .05), less total time in REM (t=-.25, p < .5), less percentage time in REM (t=-2.3, p < .05), and more time in stage 3 (t=2.2, p < .05) sleep than the comparison group. The PBD profile group also displayed a trend toward more awakenings after sleep onset (t=-2.5, p < .05) than the comparison group.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Jefferson County</th>
<th>Sample Participants</th>
</tr>
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<tbody>
<tr>
<td>Minority representation, %</td>
<td>22.3</td>
<td>28.9</td>
</tr>
<tr>
<td>Median income, $</td>
<td>39,457</td>
<td>41,375</td>
</tr>
</tbody>
</table>

Figure 1—Participant Recruitment Diagram
group. Analyses of the parent-report data indicated that the PBD profile group had significantly more remembered (\(z = 2.6, p < .1\)) and unremembered (\(z = 2.15, p < .5\)) nightmares, significantly more difficulty initiating sleep (\(z = 2.4, p < .5\)), and significantly more morning headaches (\(z = 2.2, p < .5\)).

**DISCUSSION**

Sleep disturbance has been demonstrated to have a principal role in the bipolarity of mood. The primacy of sleep disruption to state mood fluctuations has been demonstrated in adults, and sleep loss has been identified as a potential precipitating factor in manic episodes. Conversely, advancing sleep-wake schedules has been shown to improve mood in bipolar adults. Unfortunately, this relationship has not been given adequate attention, especially in the pediatric population.

This study is one of the first to examine correlates of sleep disturbance and PBD in a large community sample. Interestingly, the CBCL screening profile used in this study yielded a prevalence rate (2.97%) consistent with those reported for screening studies in the adult population (3.4%-3.7\%). Children who fit this screening profile consistently displayed differences in their sleep characteristics, even after stringent matching for age, sex, ethnicity, parent-reported ADHD, medication usage, and SDB (apnea-hypopnea events), suggesting the possibility of a specific sleep-disorder pattern associated with PBD.

No previous studies have examined PSG-related differences in young children with PBD. Our findings indicate significant quantitative differences in both PSG and parentally reported sleep characteristics between a group of children with a behavioral profile characteristic of PBD and a carefully matched comparison group, both derived from a large community sample. Results from this study suggest that children who have parentally reported disturbances in their daytime behavior (as evidenced by parental responses on the CBCL) that indicate that they are at risk for PBD also show marked disturbance in their sleep. Both PSG and parent-report data suggest sleep-continuity disturbances both at sleep onset and throughout the night. Parents of children in the PBD profile group reported significantly more remembered nightmares for their children than reported by parents of children in the control group, and PSG data show significantly less REM sleep for the PBD group than the control group. The latter result is consistent with the findings of Rao et al that adolescents who would develop a bipolar course evidenced significantly less REM sleep compared with adolescents with a major depressive disorder course. However, Rao and Dahl did not report REM-related differences between their PBD group and healthy controls.

Several methodologic issues merit comment. First, more work needs to be conducted to establish the validity of using the CBCL 3-point profile as an instrument to screen for potential PBD disorder. Continued cross-validation using standardized assessments in clinical populations will be crucial to establish the diagnostic utility of such an approach. Second, it is critical to note that 5 of the 13 children in the PBD profile group had parentally reported ADHD. This is not surprising given the high comorbidity between ADHD and PBD and the possibility that many children with PBD are misdiagnosed with ADHD. Importantly, we chose to match children with ADHD diagnoses in the PBD profile group to control children with ADHD diagnoses versus matching them to healthy controls, minimizing the likelihood that the results could be attributable to ADHD alone.

A notable limitation to this study is the small size of the PBD profile sample. It is important to recognize however, that the community sample from which this group was derived was quite large (\(N = 438\)) and that prevalence rates from the larger sample are in the range consistent with what is found in the adult population.

While the design of this study did not allow for standardized diagnostic classification of PBD, the value of the present investigation is that it enabled examination of the correlates of PBD in a large pediatric community cohort, thus providing preliminary external validity for the CBCL 3-point profile as a screening instrument, as well as initial information regarding community prevalence and the subjective and objective sleep characteristics that may be associated with the disorder. Controversy continues throughout the research and clinical community regarding the diagnostic legitimacy of prepubertal bipolar depression. There is, however, little doubt that the children in question, like the children in our PBD profile group, represent a group with severe psychopathology. At the very least, we have shown that children with a CBCL profile indicative of severe psychopathology demonstrate quantitative differences in sleep characteristics.

Although sleep disturbance is a defining feature of bipolar depression, this relationship has yet to receive sufficient attention. Our study is the first to examine sleep characteristics associated with children who may be at risk for PBD within a large community sample. Preliminary evidence from this study supports the clinical utility of including both the CBCL screening

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**Table 2—Descriptive Statistics for Age, Apnea-Hypopnea Index, and Child Behavior Checklist T Scores**

<table>
<thead>
<tr>
<th></th>
<th>PBD Profile (n=13)</th>
<th>Control (n=13)</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>6.7 ± .67</td>
<td>6.6 ± .62</td>
</tr>
<tr>
<td>AHI, events/h</td>
<td>1.8 ± 2.4</td>
<td>1.7 ± 2.4</td>
</tr>
<tr>
<td>Child Behavior Checklist, T scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxious/Depressed</td>
<td>77 ± 3.7</td>
<td>54 ± 5.8</td>
</tr>
<tr>
<td>Attention Problems</td>
<td>80 ± 6.9</td>
<td>62 ± 10</td>
</tr>
<tr>
<td>Aggressive Behavior</td>
<td>83 ± 7.4</td>
<td>61 ± 9.5</td>
</tr>
</tbody>
</table>

Values are presented as means ± SD. PBD refers to pediatric bipolar disorder; AHI, apnea-hypopnea index.

**Table 3—Polysomnography Variables in PBD Profile Group and Matched Controls**

<table>
<thead>
<tr>
<th></th>
<th>Latency to Sleep Onset</th>
<th>Control Group</th>
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<tbody>
<tr>
<td>Latency to Sleep Onset</td>
<td>38.35 (32.37)</td>
<td>28.65 (28.05)</td>
</tr>
<tr>
<td>Sleep Efficiency*</td>
<td>84.84 (11.41)</td>
<td>93.38 (5.04)</td>
</tr>
<tr>
<td>Latency to REM Onset</td>
<td>161.69 (73.28)</td>
<td>112.23 (46.91)</td>
</tr>
<tr>
<td>Total Time in REM*</td>
<td>96.5 (41.46)</td>
<td>132.46 (36.35)</td>
</tr>
<tr>
<td>Percentage Time in REM*</td>
<td>21.02 (8.43)</td>
<td>26.6 (5.89)</td>
</tr>
<tr>
<td>Stage 1 Sleep</td>
<td>9.25 (8.69)</td>
<td>10.03 (8.08)</td>
</tr>
<tr>
<td>Stage 2 Sleep*</td>
<td>51.43 (10.84)</td>
<td>45.9 (8.23)</td>
</tr>
<tr>
<td>Stage 3 Sleep*</td>
<td>6.04 (2.86)</td>
<td>3.8 (2.08)</td>
</tr>
<tr>
<td>Stage 4 Sleep</td>
<td>13.19 (6.85)</td>
<td>14.32 (7.34)</td>
</tr>
<tr>
<td>Awakenings†</td>
<td>44.67 (58.85)</td>
<td>6.92 (7.03)</td>
</tr>
</tbody>
</table>

*Significance at p < .05
†Significance at .05 level

Values are presented as mean (SD) PBD refers to pediatric bipolar disorder; REM, rapid eye movement.
measure and sleep data as part of a comprehensive evaluation of PBD. Because bipolar disorder is cyclic, it will be important for future research to examine how sleep characteristics change in association with bipolar cycling. However, the identification of discrete mood phases in children may be difficult, if not impossible, because of the ultradian cycling found in prepubertal children, which is characterized by mixed rather than discrete mood states. Innovative methodology using actigraphy, called ecological momentary assessment, which provides in-vivo information regarding sleep-wake state and mood fluctuations throughout the day is in development17 and shows much promise in its application to this population. Because sleep-wake state disruption is a principal feature and diagnostic marker for the disorder in adults as well as children and because sleep disruption has been associated with episode onset in adults,24 it is crucial that this relationship receive further attention in the pediatric population.

ACKNOWLEDGEMENTS

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