Sleep Disturbances in Young Subjects with Visual Dysfunction

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Purpose: To determine whether the type of ophthalmic disease is predictive of sleep and wakefulness disturbances in young subjects with visual dysfunction.

Design: Prospective cohort study.

Participants and Controls: Twenty-five subjects (ages 12–20) were recruited from the Missouri School for the Blind. Twelve controls with normal sight were recruited from a residential school.

Methods: Daily activity was monitored for 14 days using wrist actigraphy. Sleep and wakefulness measures were derived from actigraphy records by automated analysis. Visually impaired subjects were prospectively stratified by presence or absence of optic nerve disease.

Main Outcome Measures: Daytime napping and regularity of awakening time (wake-up time instability).

Results: Subjects with optic nerve disease napped in the daytime significantly more than other visually impaired children or normal sighted controls: 28.1 ± 4.0 minutes per day (mean ± standard error) versus 11.9 ± 2.4 minutes per day in equally visually impaired subjects with intact optic nerve function versus 6.2 ± 2.2 minutes per day in subjects with normal sight (P < 0.0001). These subjects also showed significantly more variable awakening times than the other groups. Logistic regression revealed that subjects with optic nerve disease are 9.1 times more likely to demonstrate daily napping of more than 20 minutes per day than equally blind subjects without optic nerve disease (95% confidence interval [CI] = 1.4–58.7, P = 0.02). Blind subjects with optic nerve disease are 21.3 times more likely than children with normal sight to nap more than 20 minutes on average per day (95% CI = 1.2–378, P = 0.04).

Conclusions: Optic nerve disease is predictive of increased daytime napping in young visually impaired subjects, suggesting that the nature and presence of ophthalmic disease affect the probability of concomitant sleep timing disorders. Ophthalmology 2004;111:297–303 © 2004 by the American Academy of Ophthalmology.
Materials and Methods

Twenty-five visually impaired children and young adults (ages 12–20) were recruited from the Missouri School for the Blind, a residential school. Twelve subjects with normal sight were recruited from the Thomas Jefferson boarding school. The students were prospectively placed into 3 groups based on established visual diagnosis, confirmed through a complete eye examination: (1) optic nerve disease (n = 11), (2) visual impairment without evidence of optic nerve disease (n = 14), and (3) normal sight (n = 12). The optic nerve disease group included subjects with end-stage glaucoma (n = 4), retinopathy of prematurity with long-standing bilateral stage 5 disease (n = 4), optic nerve hypoplasia (n = 2), and bilateral optic nerve trauma (n = 1). The intact optic nerve group included subjects with aniridia without glaucomatous field changes (n = 4), Leber’s congenital amaurosis (n = 2), other inherited retinal dystrophies (n = 2), prenatal stroke (n = 2), retinitis pigmentosa (n = 1), bilateral histoplasmosis (n = 1), congenital cataracts (n = 1), and occipital lobe trauma (n = 1). Exclusion criteria included major depression; severe mental retardation; sleep apnea; obesity; current use of psychoactive agents, sleeping aids, benzodiazepines, or sedating antihistamines; and illness that prevented school attendance. Specifically, no students enrolled in the study carried diagnoses of attention deficit disorder or Asperger’s syndrome.

Students boarded in school for the duration of the wrist actigraphy. The Missouri School for the Blind employed a single centralized wake-up bell at 7 AM on weekdays, but had no bell on weekends. Students in the Thomas Jefferson School were responsible for their own alarm clocks. Course schedules and available extracurricular activities were comparable between schools. Upon enrollment, each subject was fitted with a wrist actigraphy watch (Actiwatch, Mini-Mitter, Bend, OR). Each subject wore the watch continuously for 14 days. Each day, the subject would additionally log waking time, bedtime, number of night-time awakenings, naps, and number of caffeinated beverages consumed. Subjects were asked to limit their consumption of caffeinated drinks to 1 per day.

At the end of the study, the subject’s activity was evaluated using automated analysis (Actiware, Mini-Mitter). A validated algorithm that has been employed in both adult and pediatric patient populations was used to distinguish sleep versus wakefulness. This algorithm has been shown to have a 95% concordance with electroencephalographically measured sleep onset and wake onset.13 The algorithm uses the number of wrist motions in a minute plus a weighted value of motions in the previous and subsequent 2 minutes and compares this to a threshold value. When 5 consecutive minutes are scored as sleep, that period is scored as the beginning of a sleep period.

Before being monitored, each student answered a sleep quality questionnaire. Fifteen questions relating to sleep/wake behavior problems (e.g., arrived late to class due to oversleeping, difficulty falling asleep, needed more than a reminder to get up in the morning) were scored on a 5-point scale based on their responses ranging from “every day” (5 points) to “never” (1 point).14 A higher score indicates greater sleep pathology. A separate section of the questionnaire assessed depression through use of the Kandel & Davies depressive mood scale.15

The primary outcome measures were average daytime napping time and wake-onset instability. Secondary outcome measures included sleep latency, night-time awakenings, sleep duration, and sleep quality questionnaire score. Each outcome measure was compared as a 1-way analysis of variance (ANOVA). When the assumptions of ANOVA were not met, the data were converted to ranked data before ANOVA was conducted. A logistic regression analysis was performed using eye disease, visual acuity, and age as covariates. Statistical tests were considered significant when α was less than 0.05. Comparisons among the 3 groups were performed using a statistical package (SAS 8.2, SAS Institute Inc., Cary, NC).

The study was a single-center trial conducted in compliance with the Declaration of Helsinki and with approval from the Human Studies Committee of Washington University School of Medicine and the superintendents of the Missouri School for the Blind and the Thomas Jefferson School. Written consent was obtained from each participant and legal guardian after the purpose and methods were clearly explained.

Results

Full 14-day datasets were obtained on 37 subjects. One dataset from a visually impaired subject was lost due to a lost activity watch. Demographic information for the 11 visually impaired subjects with optic nerve disease, 14 visually impaired subjects with intact optic nerves, and 12 subjects with normal sight is shown in Table 1. All 3 groups were similar in age. No subjects were excluded based on a screen for depression, medication use, or illness. Thirty-six of the 37 subjects in the study reported 1 caffeinated beverage per day or less. One student had 2 caffeinated drinks in a 24-hour period on 2 separate occasions, but his sleep pattern on these 2 days was consistent with the rest of his recording.

Visual acuity was statistically indistinguishable between the 2 visually impaired groups. Statistical analysis of visual acuity differences was performed using logarithm of the minimum angle of resolution (logMAR) transformation of Snellen acuity to accurately compare visual acuity.16 The mean logMAR acuity for the optic nerve disease group was 1.37±0.21 (± standard error [SE]), versus 1.40±0.17 in the visually impaired group without optic nerve disease (Fig 1). There were 3 subjects with light perception (LP) vision and 1 subject with no LP in the optic nerve disease group, versus 4 subjects with LP vision and 1 with no LP in the group without optic nerve disease.

All groups were exposed to a similar amount of light, as measured by an irradiance detection meter built into the activity watch. The optic nerve disease group was exposed to 2 003 219±328 067 (± SE) lux–minutes per day, the blind subjects without optic nerve disease to 1 950 611±248 784 lux–minutes per day, and the normal sight group was exposed to 1 448 190±168 652 lux–minutes per day.

Daytime napping has been suggested to be a good marker of circadian desynchronization.17 Measured on a napping time per day basis, total napping in the blind patients with optic nerve disease was 28.1±4.0 minutes per day (± SE), compared with 11.9±2.4 minutes per day in visually impaired subjects without optic nerve disease and 6.2±2.2 minutes per day in the normal sight group (Fig 2). One-way ANOVA demonstrated that the blind patients with optic nerve disease had significantly more nap time per day than the other groups (P<0.0001). The average number of naps per day for the optic nerve disease group was 0.49±0.33 (mean ± SD; i.e., an average of approximately 1 nap every other day), versus 0.30±0.19 for the blind subjects without optic nerve disease group and 0.20±0.12 for the normal sight group (P = 0.05). In addition to napping more frequently, blind subjects with optic nerve disease also took significantly longer naps; the average duration of each nap was 56.9±32.3 minutes for the optic nerve disease group, 39.7±29.3 minutes for the intact optic nerve group, and 31.0±20.2 minutes for the normal sight group (P = 0.03).

Average daily nap times in excess of 20 minutes are thought to reflect pathologic sleepiness.18 We performed a logistic regression analysis to evaluate the contribution of the variables of subject age, visual acuity, and nature of ophthalmic disease (i.e., patient group)
for the presence of daytime napping longer than 20 minutes per day. Only the presence or absence of optic nerve disease was found to be a significant predictor of daytime napping. Subjects with optic nerve disease were 9.1 times more likely to have longer than 20 minutes of daily napping than visually impaired children without optic nerve disease (95% confidence interval [CI] = 1.4–52, \( P = 0.02 \)) and 21.3 times more likely than sighted children to take more than 20 minutes of daytime nap(s) each day (95% CI = 1.2–378, \( P = 0.04 \)). As shown in Figure 2, 8 of 11 subjects with optic nerve disease exceeded an average of 20 minutes of nap time per day, compared with 3 of 14 blind subjects without optic nerve disease and 1 of 12 subjects with normal sight.

Wake time instability—how regular wake-up times are on a day-to-day basis—may be employed as a surrogate marker for entrainment of the circadian clock. Wake-up times as measured by actigraphy were converted into minutes after midnight. Each individual’s standard deviation of the wake-up times from 14 days of recording was used as a measure of wake time instability. This measurement thus represents the average daily variance in wake-up time. Wake-up time instability measurements were 83 ± 10 minutes (mean ± SEM) in the optic nerve disease group, 48 ± 6 minutes in the visual impairment with an intact optic nerve group, and 56 ± 8 minutes in the normal sighted group (Fig 3). The blind subjects with optic nerve disease exhibited significantly greater wake-up time instability than the other groups by 1-way ANOVA and post hoc Tukey test (\( P = 0.02 \)).

Three subjects became blind after early childhood (1 with bilateral optic nerve trauma in the optic nerve disease group, and 1 with bilateral ocular histoplasmosis and 1 with cortical trauma in the non–optic nerve disease group). This number was too small, statistically, to test whether sleep disorders were more likely in congenital or acquired disease. Inclusion or exclusion of this subgroup did not change the statistical significance of napping time or wake-up time instability measurements between groups with and without optic nerve disease.

Table 1. Group Demographics

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yrs)</th>
<th>Depression Score</th>
<th>Visual Acuities (Better Eye)</th>
<th>Diagnoses (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual impairment with optic nerve disease</td>
<td>16.0 ± 1.9 (12–20)</td>
<td>1.7 ± 0.6 (1.0–2.2)</td>
<td>(NLP-20/100)</td>
<td>End-stage glaucoma (4), retinopathy of prematurity bilateral stage 5 (4), optic nerve hypoplasia (4), bilateral optic nerve trauma (1)</td>
</tr>
<tr>
<td>Visual impairment with an intact optic nerve</td>
<td>15.9 ± 2.4 (14–19)</td>
<td>1.6 ± 0.5 (1.0–2.2)</td>
<td>(NLP-20/40)</td>
<td>Aniridia without glaucomatous field changes (4), Leber’s congenital amaurosis (2), retinal dystrophy (2), prenatal stroke (2), retinitis pigmentosa (1), histoplasmosis (1), congenital cataracts (1), occipital lobe trauma (1)</td>
</tr>
<tr>
<td>Normal sight</td>
<td>15.5 ± 2.9 (12–17)</td>
<td>1.5 ± 0.7 (1.0–2.0)</td>
<td>(20/20–20/15)</td>
<td>Normal sight (12)</td>
</tr>
</tbody>
</table>

NLP = no light perception.
Values given as mean ± standard deviation, ranges in parentheses.

Figure 1. Distribution of logarithm of the minimum angle of resolution (logMAR)–transformed visual acuities in subjects with optic nerve disease and subjects who are blind but retain a healthy optic nerve. The middle bar represents the mean, and the top and bottom bars represent the upper and lower limits of the standard error.

Figure 2. Distribution of average napping per day in subjects with optic nerve disease, subjects blind without optic nerve disease, and subjects with normal sight. The middle bar represents the mean, and the top and bottom bars represent the upper and lower limits of the standard error.
Subjects with optic nerve disease also showed longer sleep latency than visually impaired subjects without optic nerve disease and sighted controls (Table 2). Night-time awakenings, sleep efficiency (percentage of time in bed spent asleep), and sleep duration did not significantly differ among groups. Subjective sleep quality scores were statistically indistinguishable between groups.

**Discussion**

Previous studies have suggested that visually impaired subjects are at risk for both self-reported and objectively measured sleep disorders. These sleep disorders are thought to arise, at least in part, from inability of the circadian clock to entrain correctly to external light and dark signals in visually impaired individuals. In the present field study of children and young adults with visual impairment, we confirmed that a subset of visually impaired subjects had abnormally high levels of daytime napping, increased wake-up time instability, and increased sleep latency as measured by wrist actigraphy. Logistic regression suggests that the nature of eye disease—specifically, whether the optic nerve is or is not the primary cause of disease—in large part determines the probability of pathologic levels of daytime sleepiness, as measured by daytime napping. Other patient variables, including visual acuity and subject age, are not predictive of excessive daytime napping.

Why does optic nerve disease predispose these children and young adults to excessive daytime napping and other sleep timing disorders? We suspect these subjects have difficulty entraining their circadian clocks to the external light–dark cycle. Because humans have intrinsic circadian rhythms longer than 24 hours, the clock must be continually reset to maintain synchrony with the outside world; otherwise, the body’s clock and the 24-hour day–night cycle will slowly drift out of phase, resulting in sleep and wakefulness occurring at inopportune times. Such sleep timing problems are commonly observed in blind subjects with free-running circadian rhythms. Recent studies have demonstrated that mice with outer retinal degeneration can still entrain their rhythms to light–dark cycles, whereas mice genetically engineered to lack ganglion cells cannot entrain their rhythms to light–dark cycles. Berson et al have recently described a subset of directly photoresponsive retinal ganglion cells that project specifically to nonvisual photic processing centers of the brain, including the suprachiasmatic nucleus of the hypothalamus (site of the central circadian pacemaker). Taken together, these results predict that inner retinal and optic nerve disease will be more highly associated with circadian desynchronization and resulting sleep dysfunction than will other forms of eye disease. The results of the present study support this hypothesis.

The present study has several significant limitations. First, although all blind subjects were residents of the same school (and subject to the same daily routine), the subjects with normal sight were in a different facility. Although the students at the Missouri School for the Blind had a centralized wake-up bell, the students with normal sight were allowed to set their own alarm clocks. However, as the

![Figure 3. Distribution of wake-up time instability in visually impaired children and young adults and those with normal sight. The middle bar represents the mean, and the top and bottom bars represent the upper and lower limits of the standard error. Std dev = standard deviation.](image)

<table>
<thead>
<tr>
<th>Visual Impairment with Optic Nerve Disease</th>
<th>Visual Impairment without Optic Nerve Disease</th>
<th>Normal Sight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Napping (min/day)</td>
<td>Mean 28.1 SE 4.0</td>
<td>Mean 11.9 SE 2.4</td>
</tr>
<tr>
<td>Wake-up time instability (SD)</td>
<td>83 10</td>
<td>48 6</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>37.3 5.3</td>
<td>22.1 2.6</td>
</tr>
<tr>
<td>Awakenings of &gt;5 min (no./night)</td>
<td>0.83 0.09</td>
<td>0.55 0.13</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>80.6 1.9</td>
<td>84.0 0.9</td>
</tr>
<tr>
<td>Sleep duration (hrs)</td>
<td>6.8 0.2</td>
<td>7.2 0.2</td>
</tr>
<tr>
<td>Sleep survey score</td>
<td>24.2 7.7 (SD)</td>
<td>22.2 7.8 (SD)</td>
</tr>
</tbody>
</table>
major finding in our study was that the prevalence of sleep disorders differed among blind subjects, depending on the nature of their ophthalmic disease, we do not feel that this potential confounder affects our conclusions. Second, because of limitations of the nonlaboratory setting, we did not measure more direct markers of the circadian clock phase such as daily melatonin rhythmicity or core body temperature. Thus, we can only infer that the observed increase in daytime napping and wake-up time instability is due to poor synchronization of the circadian clock. The duration and number of naps exhibited by the optic nerve disease group in the present study are consistent with values reported for blind subjects with desynchronized rhythms as measured by urinary melatonin, whereas the normal sight and blind subjects without optic nerve disease exhibited nap duration and frequency consistent with subjects previously shown to have entrained circadian clocks. Although previous studies simultaneously measuring sleep and daily profiles of urinary 6-sulfatoxymelatonin have suggested that increased daytime napping is the most sensitive clinical indicator of desynchronized rhythms, other possible causes for increased napping time, including a direct effect of light on the sleep–wakefulness system, cannot be excluded. Additionally, sleep and wakefulness were determined exclusively using wrist actigraphy. Although this method has been well validated in a number of field studies, compared with polysomnography it is insensitive for detection of more subtle features of sleep architecture, such as time spent in rapid eye movement sleep, and for detection of microarousals. Although increased daytime napping may suggest excessive daytime sleepiness, precise measurement of daytime sleepiness is better achieved using the multiple sleep latency test, in which sleep latency is measured polysomnographically at different times of the day. Further insight into the nature of the observed sleep disorders in young subjects with optic nerve disease may come from application of these laboratory-based studies to this patient population.

Although adults with visual dysfunction self-report high levels of sleep pathology, the young subjects in this study with visual dysfunction did not report a subjective problem with activities of daily living even in ideal circumstances; these difficulties are likely compounded when individuals also have significant daytime sleepiness. A clinical trial of efficacy of melatonin in improving daytime alertness in young subjects with optic nerve disease may be warranted.

Acknowledgments. The authors thank Karen Steger-May, MA, and Mae Gordon, PhD, of the Washington University Division of Biostatistics for statistical advice. They especially thank the Missouri School for the Blind and the Thomas Jefferson School for assisting in subject recruitment.

References

23. Ibuka N, Kawamura H. Loss of circadian rhythm in sleep-

Discussion
by
Alfredo A. Sadun, MD, PhD

Wee and Van Gelder have conducted a very interesting study in the best tradition of using new scientific knowledge to predict clinical features. Looking at 3 separate groups of about 12 patients each, they compared individuals who were essentially blind from outer retinal disease with those who were blind due to inner retinal impairment (loss of retinal ganglion cells) and compared both groups with 12 controls with normal sight. Their hypothesis was that patients who had suffered retinal ganglion cell loss would, due to injury of the retinal hypothalamic tract, express sleep disorders as a reflection of disturbed circadian rhythms. Their results did bear out that patients with retinal ganglion cell dysfunction were not only more likely than normals to nap, but also more likely to nap than patients with equally poor vision but in whom the damage was limited to the outer retina.

Science is hard, and science in the real world with patients can be even harder. Hence, it is not surprising that I have a few concerns and a wish list. The patients were monitored for 14 days with a wrist actigraph. This is not as clean as a biochemical measure, and the gold standard is generally melatonin levels, which can be measured from saliva samples taken throughout the day. Were the patients masked to their group? Did they have any reason to alter their routine?

These methodological issues aside, I was extremely impressed with the study. There was not only a normal control group, but also, more importantly, a second control group of patients with poor vision not due to ganglion cell dysfunction. Ideally, then, the subjects in the ganglion cell dysfunction group should all have been noted to have had optic atrophy, whereas those in the intact ganglion cell function group should have been demonstrated to have healthy optic discs.

Direct projections from the eye to the hypothalamus have been known in rats to subserve the light/dark entrainment of circadian rhythm since 1971. In 1984 we used a novel staining method (para-phenylenediamine) to demonstrate this for the first time in humans. This was later confirmed by other techniques and is now readily accepted as the anatomical substrate for the visual entrainment of diurnal rhythms. This is the pathway to blame when you fly to Europe and feel jet-lagged.

However, recent investigations demonstrate a new class of retinal ganglion cells that probably inspired this present study. There are non-image forming retinal ganglion cells that are not dependent on the usual photoreceptor (rods and cones) system, but rather can directly detect irradiance. Such retinal ganglion cells, containing a photoreceptive pigment called melanopsin, have been detected in rats. These retinal ganglion cells are thought to project directly along the optic nerve and optic chiasm to the hypothalamus to subserve the light entrainment of diurnal rhythms, pineal melatonin suppression, and even the papillary light reflex. In addition to these animal studies, it has been demonstrated that some blind human patients continue to suppress melatonin production when exposed to light. This strongly suggests that these patients, though deprived of conscious images, receive some form of visual input from their eyes. Is it possible that we can separate these blind patients who can still suppress melatonin from those who do not, on the basis of whether the injury affects the new class of retinal ganglion cells? If the injury is to the outer retina, it should not affect retinal ganglion cells, but if it is to the inner retina, then retinal ganglion cells are lost, and these specialized melanopsin-containing cells may be impaired.

The results of the present study seem robust. This is not surprising because, as the authors note, daytime napping is probably a good marker of circadian desynchronization. The authors mention that one subject had bilateral no light perception vision, and I find this particularly interesting. I would like to know more about how this patient did, because this individual probably had the least number of retinal ganglion cells left, and the question remains: how many retinal ganglion cells are needed to sustain light entrainment of the hypothalamus? Indeed, in the rat it was estimated that <1% of all retinal ganglion cells project to the hypothalamus as part of this system. Others concur that the subset of retinal ganglion cells that project to the hypothalamus are very few in number and sparse indeed. Incidentally, these melanopsin-containing cells look like type III retinal ganglion cells in that they are small and have a dendritic tree that does not arborize much, and yet extend over a very large area of the retina.

Like all good studies, this investigation answers some questions and asks others. Even though napping was seen to differ on the basis of retinal ganglion cell function, sleep duration, night-time awakenings, and sleep deficiency did not. Why should desynchro-