Background: The circadian rhythms of sleep propensity and melatonin secretion are regulated by a central circadian clock, the suprachiasmatic nucleus of the hypothalamus. The most common types of sleep disorders attributed to an alteration of the circadian clock system are the sleep/wake cycle phase disorders, such as delayed sleep phase syndrome and advanced sleep phase syndrome (ASPS). Advanced sleep phase syndrome is characterized by the complaint of persistent early evening sleep onset and early morning awakening. Although the complaint of awakening earlier than desired is relatively common, particularly in older adults, extreme advance of sleep phase is rare.

Objective: To phenotypically characterize a familial case of ASPS.

Methods: We identified a large family with ASPS; 32 members of this family gave informed consent to participate in this study. Measures of sleep onset and offset, dim light melatonin onset, the Horne-Ostberg morningness-eveningness questionnaire, and clinical interviews were used to characterize family members as affected or unaffected with ASPS.

Results: Affected members rated themselves as “morning types” and had a significant advance in the phase of sleep onset (P < .001) and offset (P = .006) times. The mean sleep onset was 2121 hours for the affected family members and 0025 hours for the unaffected family members. The mean sleep offset was 0507 hours for the affected members and 0828 hours for the unaffected members. (Times are given in military form.) In addition, the phase of the circadian rhythm of melatonin onset for the affected family members was on average 3 1⁄2 hours earlier than for the unaffected members.

Conclusions: The ASPS trait segregates with an autosomal dominant mode of inheritance. The occurrence of familial ASPS indicates that human circadian rhythms, similar to those in animals, are under genetic regulation. Genetic analysis of familial sleep and circadian rhythm disorders is important for identifying a specific gene(s) responsible for the regulation of sleep and circadian rhythms in humans.

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Advanced Sleep phase syndrome (ASPS) is characterized by persistent advanced sleep onset and awakenings that are earlier than desired.1-3 Individuals with ASPS typically experience sleepiness in the early evening, when other people are active, and early morning awakening, when most are still sleeping. Therefore, individuals with ASPS sometimes find it difficult to maintain a normal social and work life. It has been postulated that ASPS is a circadian rhythm disorder in which the phase of the circadian rhythm of sleep and wake is advanced in relation to the “normal timing,” which is synchronized, to the external environment.2,3

The search for genetic components to many complex behaviors is intensifying. The recent completion of the Human Genome Project places researchers in a better position to quickly discover genes responsible for some of these complex behaviors. A familial approach is one technique used in the field of human genetics in an attempt to find associations between behaviors and genes. To do this type of research, it is important to identify and phenotypically characterize families that exhibit these behaviors. Familial associations have been reported in several sleep disorders. There is one reported case4 of delayed sleep phase syndrome, but as yet this family has not been fully described. Restless legs syndrome, a condition in which patients experience discomfort in the legs or limbs that is relieved by movement, appears to be transmitted as an autosomal dominant trait.5 One sleep disorder in which the heritability is well established is narcolepsy. Between 1% and
SUBJECTS AND METHODS

SUBJECTS

Thirty-two members of a single family gave informed written consent before participation in this study. This study was approved by the Institutional Review Board of Northwestern University, Evanston, Ill. Subjects were interviewed and examined by a sleep specialist physician (P.C.Z.).

PROCEDURE

Identification of the ASPS phenotype and diagnosis of affected and unaffected family members were determined by physician interview using the American Sleep Disorders Association's diagnostic criteria as a guideline. The Hamilton Depression Rating Scale was administered to all subjects, and informative subjects also completed a family history questionnaire. Sleep/wake schedules were measured using wrist actigraphy and sleep diaries, the circadian preference was determined from the Horne-Ostberg morningness-eveningness questionnaire, and the circadian phase was determined from dim light salivary melatonin onset (DLMO). A family pedigree was constructed to further characterize the heritability of the disorder.

SLEEP VARIABLES

The timing and characteristics of the rest/activity cycle were determined by wrist actigraphy and sleep diaries. Subjects were asked to wear activity monitors (Cambridge Neurotechnology LTD, Cambridge, England) on the wrist of the non-dominant hand. Activity data were analyzed using a computer program (Rhythm Watch, version 2.41; Cambridge Technologies LTD) on the wrist of the non-dominant hand. Activity data were analyzed using a computer program (Rhythm Watch, version 2.41; Cambridge Technologies LTD) to plot actograms. Subjects were also asked to maintain a sleep diary during the 2 weeks of actigraphy measurement, recording bedtime, any awakenings during the night, and the final wake time.

CIRCADIAN VARIABLES

Subjects completed the Horne-Ostberg questionnaire to determine their circadian "chronotype." Scores between 70 and 86 are indicative of a morning-type; between 39 and 69, a moderate morning-type; between 42 and 58, neither type; between 31 and 41, a moderate evening-type; and between 16 and 30, an evening-type. Profiles of evening salivary melatonin level, a reliable marker of circadian phase, were collected using salivettes at 30-minute intervals under dim light conditions (<100 lux). Subjects were in dim light conditions from 1730 hours until bedtime. Sampling began at 1800 hours (central time) and was concluded at each individual's desired bedtime, which varied between individuals. (Times are given in military form.) Melatonin levels were measured using a direct radioimmunoassay (Buhlmann Saliva; ALPCO, Windham, NH). Melatonin onset was defined as the time of the first sample exceeding, by at least 2 SDs, the mean of all prior samples, without a subsequent decline to below that level.

DIAGNOSIS OR CLASSIFICATION

Subjects who met the diagnostic clinical criteria for ASPS and had a morning-type score on the Horne-Ostberg questionnaire and/or an advanced melatonin onset (those with DLMO were considered to have an advanced melatonin onset if the onset was 2 hours before that of "normal subjects" described in the literature) were considered to exhibit the ASPS phenotype.

DATA ANALYSIS

Unpaired t tests were used to determine any difference between affected and unaffected family members for self-reported sleep onsets, offsets, and durations.

RESULTS

The Family Pedigree

A pedigree of the family, shown in Figure 1, was constructed from the physician interviews, sleep questionnaires, and family histories. Thirty-two family members were studied. Eight family members were diagnosed as being definitely affected, 4 as being possibly affected, and 8 as being affected by history; 12 were unaffected. The members studied ranged in age from 11 to 85 years. The age of onset (by history) varied from as early as 8 years to early adulthood.

The proband was an 85-year-old man with a history of going to sleep in the early evening and awakening in the early morning for as long as he could remember. He reported that his children and several other relatives had a similar sleep pattern. The ASPS phenotype can be seen in 4 generations of the proband's branch and in possibly 3 generations in an extended branch. The pattern of affected individuals in the proband's branch is consistent with a genetic model of segregation of a single autosomal dominant gene. The ASPS status of some individuals in an extended branch of the family is considered to be possibly

2% of narcoleptic probands have family histories of excessive daytime sleepiness. Furthermore, human narcolepsy has been linked to a region of the major histocompatibility complex (HLA) genes. More recently, the compound orexin has been linked to narcolepsy. Using a narcoleptic dog model, Lin and colleagues recently showed that the hypocretin (orexin) receptor gene (Hcrt) may be responsible for narcolepsy. Chemelli and colleagues found that orexin knockout mice exhibit a phenotype similar to that seen in narcoleptic patients and in dogs that have a mutation of canucr-c-1, a canine narcolepsy gene.

In comparison, ASPS appears to be a far more rare sleep/circadian rhythm disorder, and until recently there were only 3 reported cases of ASPS. More recently, however, Jones and colleagues described 3 separate families with a familial preponderance of ASPS. Identification of the familial nature of ASPS suggests a genetic basis for this disorder. The present study phenotypically characterizes an additional case of familial ASPS by describing the clinical characteristics, activity/rest measures, and circadian phase in affected and nonaffected members of a large family with ASPS.
affected. The oldest member of this branch is an elderly woman who by history is affected, but because of her poor health, accurate characterization of the disorder was not possible. However, we do consider her to be affected by history. Her daughter is self-reported as affected, and her granddaughter is a teenager and is advanced compared with other adolescents in the general population, but does not strictly meet the American Sleep Disorders Association criteria for ASPS.

Data from the completed interviews, the Hamilton Depression Rating Scale (mean [± SD] score, 2.4 [± 2.7]), and sleep questionnaires do not indicate that the ASPS phenotype is associated with a high prevalence of affective disorder or other types of sleep disorders, such as narcolepsy, sleep apnea, restless legs syndrome, or periodic leg movements. Results from a clinical sleep study indicated that 1 subject does have sleep apnea.

SLEEP/WAKE PATTERNS

Representative profiles of wrist activity records for affected subjects can be seen in Figure 2, left. The wrist activity monitoring clearly shows that family members affected with ASPS have early sleep onsets and offsets. The average subjective sleep onsets, offsets, and durations were calculated for 10 individuals and are shown in Table 1. Relative to unaffected subjects, affected subjects had, on average, sleep onsets nearly 3 hours earlier and sleep offsets nearly 3½ hours earlier. The mean sleep duration was not significantly different between the 2 groups.

CIRCADIAN PHASE

Horne-Ostberg Questionnaire of Diurnal Preference

Scores on the Horne-Ostberg questionnaire are shown in Table 2. All affected individuals were morning types, while none of the unaffected individuals were morning types.

Dim Light Melatonin Onset

Dim light melatonin onset values were collected via saliva sampling from 4 affected and 1 unaffected family member from the proband’s branch of the family (Figure 2, right). Although no statistical analysis of these findings can be carried out due to the limited number of samples in each group, the mean DLMO for the affected subjects was much earlier (1830 hours) than that of the unaffected subject (2200 hours). There was an advance in the DLMO of the affected individuals of approximately 3½ hours compared with that of the unaffected family member. The phase of melatonin onset for the individuals with ASPS was advanced when compared with that seen in the normal population.18

COMMENT

We have identified a large family with ASPS in which an affected member is present in every generation, suggesting that the ASPS phenotype segregates as a single gene with an autosomal dominant mode of inheritance (Figure 1). Analysis of sleep diary and activity records indicates that affected family members have significantly earlier sleep onsets and offsets than unaffected members. The results are consistent with those of published reports12,14 of individual cases of ASPS. However, there was no significant difference between the 2 groups in sleep duration. This is consistent with ASPS criteria and published reports12,16,19 of polysomnographic recordings that show no difference in the duration and architecture of sleep between affected and unaffected individuals. These results suggest that ASPS is not likely due to a disruption of sleep homeostasis or sleep architecture, but rather
represents an alteration of the circadian timing of sleep propensity.

When we examined subjective circadian measures (Horne-Ostberg morningness-eveningness questionnaire scores), the results indicated that all family members who were considered affected with ASPS also scored as morning-type on the questionnaire, whereas the unaffected members scored as moderate evening types or fell into neither category. Morning-type on this questionnaire has generally been associated with an advance in other circadian rhythms, including core body temperature and performance levels.20,21 A link has also been suggested between diurnal preference, as determined by the Horne-Ostberg questionnaire, and a polymorphism located in the 3' flanking region of the human CLOCKS gene.22 (CLOCK is a basic helix-loop-helix transcription factor that, when mutated, alters the circadian period.)

It could be suggested that a genetic component of diurnal preference could be passed on through a family similar to the one described herein.

In addition, our objective measure of circadian phase, DLMO, clearly showed that members of this family with the ASPS phenotype have an earlier DLMO than either the unaffected family member or unaffected individuals described in the literature.18,23

Since there are only a few reported cases of ASPS, it would appear to be a relatively rare disorder. However, several factors, such as the lack of complaints from these individuals and the lack of recognition of this condition by health care professionals, may explain this low incidence of reported cases.24 Several of the participants interviewed in this study were accustomed to their advanced schedule and were surrounded by many members of their family who were similarly affected. In addition,
individuals with ASPS found that social pressures, such as work schedules, adhered to this advanced phase and were, therefore, resigned to the timing of their sleep/wake schedule. However, it is unlikely that the advanced sleep phase is merely a result of social conditioning within a family unit. Interviews reveal that several members of the same family unit are affected with ASPS; however, there are spouses and siblings within the same family unit, living in the same house, who do not exhibit the advanced sleep phase.

Identification of the ASPS phenotype may have been influenced by the effects of marriage to individuals with a delayed sleep phase ("night owls"). This was the situation in individuals from the extended branch whose spouses were reported to be night owls. Another consideration in regard to accurate identification of the affected status in this familial case of ASPS is the broad age range of its members. Changes in circadian timing and in the timing of sleep are associated with age.²⁵,²⁶ Specifically, there is generally an advance in sleep/wake behavior for older people and a delay in teenagers.²⁵-²⁷ When the teenaged affected family members were compared with the rest of the population in their own age group, they were advanced. However, they did not meet the American Sleep Disorders Association criteria when sleep onsets and offsets were assessed.¹ Research diagnostic criteria of ASPS need to be established and defined, perhaps taking into account age. This is most crucial for the accurate characterization of circadian phase syndromes. With this in mind, in the present study, we used the American Sleep Disorders Association criteria as a guideline for determining the phenotype of ASPS, but we also used other tools, such as morningness-eveningness preference and melatonin onset, as more stringent measures of circadian phase. Individuals with an advanced sleep phase also displayed an advance in other circadian rhythms, indicating that this condition is best described as advanced circadian phase syndrome.

This family, along with the 3 families identified by Jones et al., suggests that not only is ASPS familial in some cases but that it may be more prevalent than previously believed. The results reported for this family and those of Jones et al appear to be consistent and segregate in a similar pattern: the sleep onsets and Horne-Ostberg questionnaire scores are similar. Although Jones et al do report a DLMO of on average 1 hour earlier than ours, this could be the result of a later period of dim light exposure before sampling in our studies. We have yet to determine whether there are changes in period in members of this family like that reported in a single case by Jones et al.

Taken together, the results from the present study indicate that ASPS may in some cases be a familial disorder that appears to segregate as a single gene with an autosomal dominant mode of inheritance. Identification of families with alterations in circadian sleep phase is expected to play an important role in identifying the gene(s) responsible for regulation of human sleep and circadian rhythms.

Table 1. Average Subjective Sleep Onsets, Offsets, and Durations for 5 Affected and 5 Unaffected Subjects*  

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>ASPS Status†</th>
<th>Onset§</th>
<th>Offset§</th>
<th>Duration, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>2201 (± 0)</td>
<td>0508 (± 0037)</td>
<td>7.14 (± 0.63)</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>1901 (± 0049)</td>
<td>0214 (± 0114)</td>
<td>7.00 (± 0.64)</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>2230 (± 0)</td>
<td>0521 (± 0044)</td>
<td>6.96 (± 0.75)</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>0057 (± 0019)</td>
<td>0707 (± 0046)</td>
<td>6.28 (± 0.75)</td>
</tr>
<tr>
<td>5</td>
<td>−</td>
<td>0012 (± 0038)</td>
<td>0904 (± 0103)</td>
<td>8.86 (± 1.03)</td>
</tr>
<tr>
<td>6</td>
<td>−</td>
<td>0130 (± 0024)</td>
<td>0925 (± 0127)</td>
<td>7.93 (± 1.30)</td>
</tr>
<tr>
<td>7</td>
<td>−</td>
<td>0237 (± 0051)</td>
<td>0912 (± 0146)</td>
<td>7.50 (± 1.87)</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>2142 (± 0026)</td>
<td>0606 (± 0032)</td>
<td>8.40 (± 0.89)</td>
</tr>
<tr>
<td>9</td>
<td>+</td>
<td>2130 (± 0024)</td>
<td>0645 (± 0017)</td>
<td>9.25 (± 0.50)</td>
</tr>
<tr>
<td>10</td>
<td>+</td>
<td>2125 (± 0028)</td>
<td>0730 (± 0143)</td>
<td>9.63 (± 1.65)</td>
</tr>
<tr>
<td>11</td>
<td>−</td>
<td>0130 (± 0024)</td>
<td>0925 (± 0127)</td>
<td>7.93 (± 1.30)</td>
</tr>
<tr>
<td>12</td>
<td>−</td>
<td>0237 (± 0051)</td>
<td>0912 (± 0146)</td>
<td>7.50 (± 1.87)</td>
</tr>
</tbody>
</table>

*For all affected subjects, the mean (± SD) sleep onset was 2121 (± 0121) hours; sleep offset, 0507 (± 0108) hours; and sleep duration, 7.73 (± 1.05) hours. For all unaffected subjects, the mean (± SD) sleep onset was 0025 (± 0132) hours; sleep offset, 0828 (± 0104) hours; and sleep duration, 8.04 (± 1.29) hours. The differences between affected and unaffected subjects were significant for sleep onset (P = .001) and sleep offset (P = .006) and not significant for sleep duration (P = .69).
†ASPS indicates advanced sleep phase syndrome; +, affected; and −, unaffected.
‡Data are given as mean (± SD).
§Data are given as hours of the day or night (military form).

Table 2. Horne-Ostberg Morningness-Eveningness Questionnaire Results for 10 Family Members  

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>ASPS Status†</th>
<th>Questionnaire Score</th>
<th>Type (Morning or Evening)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>+</td>
<td>75</td>
<td>Morning</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>85</td>
<td>Morning</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>66</td>
<td>Moderate morning</td>
</tr>
<tr>
<td>5</td>
<td>−</td>
<td>58</td>
<td>Neither</td>
</tr>
<tr>
<td>7</td>
<td>−</td>
<td>45</td>
<td>Neither</td>
</tr>
<tr>
<td>8</td>
<td>−</td>
<td>36</td>
<td>Moderate evening</td>
</tr>
<tr>
<td>9</td>
<td>−</td>
<td>52</td>
<td>Neither</td>
</tr>
<tr>
<td>10</td>
<td>+</td>
<td>73</td>
<td>Morning</td>
</tr>
<tr>
<td>11</td>
<td>+</td>
<td>55</td>
<td>Moderate morning</td>
</tr>
<tr>
<td>12</td>
<td>−</td>
<td>46</td>
<td>Neither</td>
</tr>
</tbody>
</table>

*The mean (± SD) questionnaire score for all affected subjects was 72.5 (± 9.0); for all unaffected subjects, 44.8 (± 6.7). The difference between affected and unaffected subjects was significant (P = .002).
†ASPS indicates advanced sleep phase syndrome; +, affected; and −, unaffected.

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