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Sleep Medicine 3 (2002) 177–178

SLEEP MEDICINE

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Journal search and commentary

Article reviewed: Familial advanced sleep phase syndrome ☆

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Accepted 4 January 2002

Objective

Phenotypically characterize a large kindred with the circadian sleep disorder: advanced sleep phase syndrome (ASPS).

Study design

Descriptive study including clinical, actigraphic and melatonin measurements.

Study population

The large family (32 members) of an 85 year-old proband. The family was known to include several with advanced sleep phase syndrome.

Methods

Family members were interviewed and examined by a sleep specialist physician and categorized for a ASPS phenotype according to the ICSD criteria. The Hamilton Depression Rating Scale was administered to all subjects. Sleep/wake schedules were measured using wrist actigraphy and sleep diaries, the circadian preference was determined from the Horne–Ostberg morningness/eveningness questionnaire (to evaluate the circadian chronotype) and the circadian phase was measured from dim light salivary melatonin onset (DLMO) obtained from 30-min interval sampling (starting at 18:00 h) collected in dim light condition from 17.30 h. Melatonin onset was defined as the time of the earliest sample exceeding by 2 standard deviations the mean of prior samples. Subjects meeting the clinical criteria for ASPS and a morning-type score on the Horne–Ostberg questionnaire and/or a DLMO starting at least 2 h before the 'normal' onset-time (according to literature data) were considered affected by ASPS. A family pedigree was constructed by the clinical data to characterize and determine the familial pattern of the syndrome. Unpaired *t*-test was used to determine significant differences between affected and unaffected subjects for sleep measures (diaries)

Results

Out of the 32 members, eight were definitely considered to have ASPS, four possibly had ASPS and eight had a clinical history of ASPS without any other indication for ASPS. Twelve family members did not have ASPS. The ASPS phenotype occurred in four generations of the 85 year-old proband's relatives and in three generations in an extended family branch. The familial pattern in the proband branch indicated single autosomal dominant pattern of gene segregation.

The Hamilton Scale results do not indicate a significant prevalence of affective disorder and the sleep clinician interview also failed to find other sleep disorders in the family. (The clinical histories identified only one member with another possible sleep disorder, OSA).

Sleep/wake patterns (by actigraph and diaries) indicated that affected subjects had an earlier sleep onset (3 h on average) and sleep offset (3 1/2 h on average) compared to unaffected subjects, without any difference in sleep duration between the two groups.

Circadian chronotype results showed all the affected members ranking in the 'morning type' or 'moderate morning-type' score of the questionnaire.

DLMO (collected only in one unaffected and four affected subjects) was earlier in the four ASPS (18.30) compared to the one unaffected (22.00) and also advanced compared to data from the literature.

☆ Reid KJ, Chang AM, Dubocovich ML, Turek FW, Takahashi JS, Zee PC. Arch Neurol 2001;58:1089–1094.

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PII: S1389-9457(02)00020-5

Conclusion

The presence of an affected member for all four generations indicated a single gene autosomal dominant mode of inheritance for the ASPS in this family. Despite the lack of polysomographic recording of sleep, clinical and objective measures of circadian phase and sleep/wake pattern indicated the real presence of an advanced 'biological clock' in affected members, which could not be explained as resulting from social, work or family conditions. In some cases, although rarely according to the literature, ASPS, like other sleep disturbances, may be a genetic familial disorder.

Comment

ASPS, a disorder characterized by a very early sleep onset and offset with normal length and quality of sleep, is rare. Only a very few sporadic cases have been described up to now, and three kindred with members affected by a profound advance of sleep/wake, melatonin and temperature rhythms were reported only recently [1]. Thus, this family is the fourth described in the literature and, despite some flaws in the methodology of studying the subjects, confirms the possibility that a disorder of the sleep-wake rhythm may be inherited. This family was well characterized both from the clinical and sleep/wake schedule points of view. The paper, when considered with the report of other similar cases by Jones et al. [1] and the description of a familial delayed sleep phase syndrome [2], provides further strong support for the view that variations in phases of human circadian rhythms, like those in animals, are genetically controlled.

From a clinical point of view it has to be stressed that this family has a disorder less marked than the other families reported in literature. The scores on the Horne–Ostberg questionnaire were generally lower, and in some affected members were under the limits considered an indication of full morningness chronotype. The DLMO is on average below expectation and the actigraphic record of one affected subject does not appear striking. However, considering the number of possibly affected members and putatively affected candidates, the magnitude of the occurrence in this family and the clear pattern of inheritance are strongly consistent with an autosomal dominant trait, as previously suggested [1].

From a genetic point of view this paper compliments the recent report of the localization of the familial ASPS gene near the telomere of the chromosome 2q [3].

Genetic studies by induced mutagenesis, or by interaction of the molecular component of the oscillator (SCN neurons) with a component identified by mutagenesis, and recognition of spontaneous mutations in *Drosophila*, fungi, plants and animals, led to the identification and characterization of clock genes responsible for circadian behaviors. Four proteins have been found (CLOCK and BMAL1, PER and TIM) which by their interaction could determine circadian oscillation in mammals as well. The encoded proteins due to these genes composed of PAS domain transcription factors are controlled by regulatory phosphoproteins (PERIOD and CRYPTOCHROME). One of the candidate genes to control circadian rhythms in humans (h*Per2*), homologous of the PERIOD gene in *Drosophila*, is located on chromosome 2q and was revealed mutated in affected members of one family with ASPS [3]. A missense mutation (probably a loss-of-function mutation) in a region of h*Per2* (which causes an hypophosphorylation in vitro) is responsible for an alteration of the circadian period in humans. Human *Per2*comprises 23 exons, and the sequences of exon 17 led to the identification of changes predicting a substitution of a serine at aminoacid 662 with a glycine (S662G). This mutation co segregated with all the ASPS phenotypes of one family, with the exception of one branch, and was not found in a large sample of controls [3]. Moreover the mutation led to decreased phosphorylation by a Kinase that, when mutated, generates a similar phenotype in animals. However not all the families tested, and not all the members of the same family linked with the hPer2 locus, suggesting a heterogeneity of the locus for the familial ASPS.

The genetic testing of other ASPS families, such as the one described by Reid et al., might provide further evidence that mutations in other genes may lead to the same alterations of the sleep/wake rhythm (ASPS) or to other sleep/wake disturbances such as delayed sleep phase syndrome (DSPS), hypernychthemeral syndrome, jet-lag or shift work syndromes.

Future applications of the discoveries of circadian clock genes in animals might permit identification of these or other related genes responsible for the regulation of circadian rhythmicity in human beings. Human diurnal preference has already been found to be associated with the CLOCK gene [4] and a Japanese group recently found that structural polymorphisms in the h*Per3* gene may be implicated in the pathogenesis of DSPS [5].

References

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