Rest-Activity Patterns in Children With Hypopituitarism

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ABSTRACT. Objectives. Physical lesions in the region of the suprachiasmatic nuclei, which are the site of a circadian clock, result in abnormal circadian rhythmicity in animals, yet the extent of biological rhythm problems in individuals with anatomic or functional lesions in the hypothalamic-pituitary region are largely unknown. To address this issue, we examined patterns of rest and activity of children with hypopituitarism.

Methods. Children who were between the ages of 2 and 18 years and had the diagnosis of panhypopituitarism were evaluated. Twenty children were studied, including children with septo-optic dysplasia (SOD), congenital hypopituitarism, brain tumors, closed head trauma, and head irradiation. For assessing patterns of activity, individuals wore Actiwatches for 3–4 weeks to measure patterns of gross motor activity.

Results. Seventeen children had normal patterns of rest and activity, with an average period length of 24.01 ± 0.01 hours. Three children, including 2 with SOD and 1 with a hypothalamic germinoma, showed abnormal activity patterns in which there was not consolidated rest at night. One patient with an optic glioma had nonentrained circadian phase.


ABBREVIATIONS. SCN, suprachiasmatic nuclei; SOD, septo-optic dysplasia.

The paired suprachiasmatic nuclei (SCN) located in the anterior hypothalamus are the site of a biological clock.1,2 These nuclei generate and regulate circadian rhythms, which are 24-hour rhythms that synchronize endogenous physiologic processes with the light-dark cycle.1,2 Notable examples of circadian rhythms include daily rhythms in hormone production and rest-activity (sleep-wake) cycles. Because the daily oscillations of the SCN are approximately but not exactly 24 hours, the daily oscillations of the SCN are synchronized, or entrained, to the 24-hour day.1,2 Light is the dominant entraining stimulus; nonphotic factors may also induce entrainment in some settings.3

The SCN are located at the base of the third ventricle, just above the optic chiasm. In humans and other mammalian species, the structures are very small, measuring approximately 1 × 0.1 mm.2,4 SCN rhythms seem to be driven by the complex interaction of a handful of transcriptional regulators and kinases resulting in 24-hour cycles of protein expression.1 In mammals, these factors include the proteins PERIOD, CLOCK, CRY, BMAL, and casein kinase 1 e.1

Different circadian system abnormalities are now recognized. In the absence of light or entraining stimuli and in some blind individuals, circadian rhythms will be normally expressed, yet the rhythms will “free run” and drift out of synchrony (phase) with the light-dark cycle.5 In comparison, physical lesions of the SCN result in arrhythmia, as daily sleep-wake (rest-activity) cycles, temperature, and hormone rhythms are lost.1 More recently, mutations in clock genes, including Per 2 and Clock, have been shown to result in either arrhythmia or phase disorders.1,6,7

At present, the extent of biological rhythm problems in individuals with anatomic or functional lesions in the hypothalamic-pituitary region is largely unknown, as reports describing abnormal expressed rhythmicity in individuals with hypothalamic and pituitary dysfunction are limited to a few case reports. Abnormal temperature rhythms have been reported in 1 woman with a hypothalamic tumor.8 Arrhythmia has been reported in a young boy with septo-optic dysplasia (SOD).9

To address this issue, we examined patterns of rest and activity of children with hypopituitarism. We now report that some children with hypopituitarism have abnormal daily rest-activity patterns.

METHODS

Human Subjects

All children who were between the ages of 2 and 18 years and followed by the Section of Pediatric Endocrinology at Yale Medical School with the diagnosis of panhypopituitarism were eligible for study. Individuals were included for evaluation if they had received a diagnosis by standard criteria of being deficient in 2 or more pituitary hormones and were taking 2 or more pituitary replacement hormones (hydrocortisone, thyroxine, growth hormone, depo-testosterone, estrogen/progesterin, desmopressin). The treating physicians established diagnoses. For patients with SOD, diagnoses were established by magnetic resonance imaging and ophthalmologic evaluation using standard criteria.10 All patients had at least 1 magnetic resonance imaging scan performed. The Yale University Human Investigations Committee approved these studies.
Rest-Activity Analysis

Individuals were given Acti(watches (Minimitter; Sunriver, OR) to wear on the wrist of their nondominant hand for 4 weeks. Acti(watches record a digitally integrated measure of gross motor activity that is assessed by an internal accelerometer. The watches are waterproof and shockproof. The use of Acti(watches to monitor rest-activity patterns and sleep efficiency in children and adults has been validated.12–16

The manufacturer calibrated the Acti(watches so that collection of data and sensitivity between watches were consistent with the number of activity counts recorded reflecting the degree and speed of motion. Watch sensitivity was <0.01 g-force.

Statistical Analysis

Data were analyzed to determine the time of sleep onset and waking. The ratio of activity patterns during the daytime (0700–2100 hours) and nighttime (2100–0700 hours) was also obtained. Circadian period was calculated using χ² periodogram analysis to assess periodicity (r).17 Sleep efficiency was calculated as the ratio of total sleep time to sleep period.18 Analyses were performed using Actiware software (Minimitter).

RESULTS

Twenty children met criteria for eligibility. The cohort included 4 children with SOD and hypopituitarism, 7 children with congenital hypopituitarism without SOD, 7 children with hypopituitarism as the result of brain tumors (2 craniopharyngiomas, 3 optic gliomas, 2 germinomas), 1 individual with hypopituitarism secondary to closed head trauma, and 1 child with hypopituitarism as a result of head irradiation. Two patients had total blindness (congenital anophthalmia; optic glioma). The ages of patients were 2 to 18 years; 6 were female, 14 were male.

Eighteen of the 20 the individuals who were sent the watches wore them for 4 weeks. Two of the 20 individuals wore the watches for 3 weeks. Analysis of actograms indicated that nearly all children had distinct periods of rest and activity. For the children with distinct patterns of rest and activity, the average waking time in the morning was between 0630 and 0800 hours. The time when the children seemed to go to sleep was between 2100 and 2300 hours. Sleep efficiency ranged from 88% to 95%, agreeing with values for control individuals.14–16 The ratio of daytime to nighttime activity bouts was 11.5 ± 3.2 (mean ± standard error of the mean). Period analysis revealed an average period length of 24.01 ± 0.01 hours for this group.

Three children showed evidence of abnormal activity patterns, in which there was not consolidated rest at night (Figs 1 and 2). In 2 children with SOD (ages 2 and 12 years), the children were more active during the day than at night, yet there was considerable nighttime activity (day/night ratios: 2.10 and 1.20; sleep efficiency: 63% and 55%; Figs 1 and 2C and 2D). In 1 of these children, there was profound visual impairment (20/500). In the other, the visual deficit was mild (20/100). The period lengths for these children were 24.0 and 24.1 hours, respectively. In one 17-year-old girl who had a large hypothalamic germinoma, there was also more activity during the day than at night yet considerable nighttime activity (day/night ratio: 2.3; sleep efficiency: 64%; period: 24.0 hours). It was not possible to distinguish these individuals from those with normal activity patterns on the basis of the degree of pituitary insufficiency or hormone replacement therapy.

Two patients were blind without any visual perception as a result of congenital anophthalmia in 1 adolescent and destruction of the optic chiasm caused by an optic glioma in another. Both individuals manifested distinct day/night patterns in activity (day/night ratios: 12.2 and 15.5; sleep efficiency: 90% and 91%). In the individual with the optic glioma, circadian phase seemed to free-run, as the period length was ranged from 25.3 to 23.5 hours (Fig 1F). In the individual with congenital anophthalmia, expressed rhythmicity was in synchrony with the light-dark cycles, with a period length of 24.0 hours (Fig 1E).

DISCUSSION

It is not known whether children with anterior hypothalamic lesions have functional abnormalities of the central circadian pacemaker. Our studies suggest that even in children with anatomic lesions in the hypothalamic-pituitary region, patterns of rest and activity are usually normal. However, some children will manifest abnormal patterns of rest and activity.

When we examined patterns of rest-activity, nearly all children were considerably more active during the daytime and less at nighttime. Compared with published actograms of children, adolescents, and adults,12,13,19–21 the plots of activity patterns were normal in 17 of the 20 individuals. In 3 individuals, excessive activity at night was noted, as reflected by reduced sleep efficiency. One of these individuals was a female adolescent with a large tumor involving the anterior hypothalamus. In contrast, in 6 other individuals with tumors in this region, day-night differences were more clearly apparent. Animal studies suggest that the entire SCN must be destroyed before arrhythmic behavior occurs, as there may persistent rhythmicity with near-complete SCN lesions.22 It is therefore likely that despite the presence of hypothalamic-pituitary lesions in our patients, residual SCN tissue preserved expressed rhythmicity. Even with modern imaging methods, because of the small size of the SCN, it is not possible to visualize the nuclei using noninvasive methods. Thus, we cannot assess whether the less apparent rhythmicity in the female adolescent is attributable to more extensive SCN destruction than with the other individuals.

We were especially interested to observe that 2 of the children manifesting abnormal patterns of rest-activity had SOD. We previously reported 1 child with SOD (not included in this report) who also had arrhythmic behavior patterns.9 In the 2 children with SOD included in this report, we also observed much more activity during the nighttime than is typical and the absence of consolidated periods of rest and activity.

At present, we know little about SCN anatomy in children with SOD. However, Swaab et al (personal communication; Netherlands Institute for Brain Research, Amsterdam) performed neuroanatomical...
studies in 1 child with SOD and did not find evidence of SCN neurons. This anatomic information coupled with our findings of abnormal rhythmicity in 2 of the 4 children studied here raises the possibility that SCN formation is abnormal in some children with SOD.

It is also important to note that we observed normal patterns of activity in 2 other children with SOD, who were on similar treatments for pituitary insufficiency. In the 7 children with congenital hypopituitarism without SOD, activity patterns were also normal. Thus, in the absence of SOD, congenital hypopituitarism may not be associated with abnormal rest-activity patterns.

When period analysis was performed, the length of the circadian cycle was 24.0 hours for all but 1 individual, indicating entrained rhythms. Activity patterns also were normal with period length of 24 hours even in an adolescent with congenital anophthalmia and no light perception. This observation suggests that the structured schedules imposed on children helps maintain circadian entrainment. In the other blind individual evaluated, the rest-activity pattern drifted out of phase with the solar cycle, as the period length ranged from 23.5 to 25 hours. This observation agrees with findings in blind adults without photic innervation of the SCN, who have free-running circadian rhythms. The timed administration of melatonin has been shown to be effective in helping to entrain these individuals.

We recognize that a limitation of our studies is that children were studied at home rather than in constant conditions of a hospitalized setting. Thus, patterns of rest and activity may reflect influences of parents and scheduling rather than endogenous factors. It therefore will be interesting to reexamine these children in settings where we can assess more fully endogenous clock function using other markers of circadian phase, such as humoral rhythms in melatonin and/or cortisol levels. We also recognize that our sample size is relatively small, yet considering that 4 of the 20 individuals studied had abnormal activity patterns, multicenter efforts to evaluate expressed rhythmicity in more children with hypothalamic pituitary lesions will be important.

Overall, our observations show that actigraphy is a valuable tool for assessing circadian function in children with pituitary abnormalities.

Fig 1. Actograms of rest-activity patterns in pediatric patients with hypopituitarism. Dark bars represent activity; the same activity scale is used in each plot. The time of day is shown on top. A and B, Two children with congenital hypopituitarism. C and D, Two children with SOD. E, Blindness caused by congenital anophthalmia. F, Blindness caused by optic glioma. Note the irregular patterns of rest and activity in the 2 children with SOD and free-running activity patterns in the patient with the optic glioma.
useful tool for evaluating patterns of rest and activity in children. We find that children with congenital hypopituitarism have normal patterns of rest and activity, yet children with anterior hypothalamic tumors or SOD seem to have a higher likelihood of abnormal circadian rhythmicity and warrant evaluation for abnormal patterns of expressed rhythmicity.

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