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Prevalence and risk factors for disrupted circadian rhythmicity in children with optic nerve hypoplasia

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ABSTRACT

Background/aims Children with optic nerve hypoplasia (ONH) have visual impairment and may have hypopituitarism and developmental delay. Children with ONH have also been reported to have abnormal sleep–wake cycles. We assessed the incidence and nature of sleep–wake abnormalities in children with ONH.

Methods Rest–activity patterns were assessed in 23 children with ONH using actigraphy, which is a non-invasive method for continuously monitoring activity. The children also had formal assessment of pituitary function, visual acuity measurements, assessment of pupillary responsiveness, MRI scans of the head and assessment of neurocognitive function.

Results Sufficient actigraphy data were obtained on 19 of the children. Analysis of expressed rhythmicity revealed normal rest–activity patterns in 13 children (68%). Of the six children (32%) with abnormal rhythmicity, three had fragmented sleep, one had free-running rest–activity cycles and two were arrhythmic. Of the children with normal rhythmicity, the following were found: hypoplastic corpus callosum in 30%, growth hormone deficiency in 53%, hypothyroidism in 23%, adrenal insufficiency in 30%, diabetes insipidus in 0% and developmental delay in 15%. Of the children with abnormal rhythmicity, the following were found: hypoplastic corpus callosum in 66% ($p>0.05$), severe visual impairment in 100% ($p=0.006$), abnormal pupillary responsiveness in 85% ($p=0.0084$), cognitive impairment in 100% ($p=0.04$) and multiple hormonal deficiencies in 66% ($p=0.03$).

Conclusions Abnormal rest–activity rhythmicity patterns are present in 30% of children with ONH. The best predictors of abnormal rhythmicity are severe vision impairment, abnormal pupillary responsiveness, developmental delay and multiple hormonal deficiencies.

hormone or elevated prolactin.⁴ In addition, children with ONH may have posterior pituitary disease resulting in diabetes insipidus.⁴

Reports suggest that children with ONH may have abnormal circadian rhythmicity, as disrupted sleep–wake (rest–activity) patterns have been reported in children with ONH.^{9–11} Because circadian rhythms are generated and regulated by the suprachiasmatic nuclei (SCN), which are located in the anterior hypothalamus,¹² it is possible that defects that affect the anterior hypothalamic region will disrupt the circadian system function. Such potential problems could occur if there are inadequate retinal projections to the SCN to entrain circadian clock function or if SCN development and/or function are abnormal. However, we know little about the prevalence of abnormally expressed rhythmicity in children with ONH.

To address this issue, we studied rest–activity patterns in children with ONH and looked for associated clinical risk factors.

METHODS

Human subjects

Participants were recruited from a long-term prospective study of prenatal and clinical risk factors of ONH at Childrens Hospital Los Angeles. Children were diagnosed as having ONH by a single neuro-ophthalmologist (MB). Eligible participants for the study of rest–activity cycles were enrolled in the prospective study and were at least 24 months of age. No individuals were treated with therapies that could influence sleep and wakefulness during these studies. The studies were approved by the Childrens Hospital Los Angeles Committee on Clinical Investigations and the Yale University Human Investigation Committee.

Visual acuity

Visual acuity was measured on an annual basis and the assessment performed closest to the start of wearing the Actiwatch was used for analysis. Visual acuity was measured using the Snellen eye chart, or linear 'E' or linear Allen figures in illiterate subjects. Visual acuity that could not be quantified was determined based on ability to fixate and follow or react to light. Visual acuity of the better-seeing eye was assigned one of six categories (one being the best vision) and used in analysis for the present study. Vision was categorised as follows: (1) fixation and follows (F&F) 1-inch toy at 1 foot; Snellen $\geq 20/200$; (2) F&F 6-inch toy at 1 foot; Snellen $<20/200$ – $20/800$; (3) poor fixation and ability to follow a face or large toy; Snellen $<20/800$ – $20/8000$; (4) behavioural response to motion;

Optic nerve hypoplasia (ONH) is a leading cause of paediatric vision impairment in the USA and Europe.^{1,2} It is estimated that 1 in 10 000 children are born with ONH.¹

ONH is a congenital condition that is associated with hypopituitarism.^{3–5} Affected individuals may also have brain abnormalities, such as agenesis of the corpus callosum or septum pellucidum.^{1–3} Individuals with ONH may have normal intelligence, yet the majority of affected children are developmentally delayed.^{6,7} Some children with ONH may be blind; others will have functional vision.¹

Hypopituitarism occurs in about 75% of children with ONH,⁸ and can involve deficiencies in growth hormone, adrenocorticotropin, thyroid stimulating hormone, luteinising hormone, follicle stimulating

(5) behavioural response to light; (6) no visual behaviour.
The visual acuity of the better eye was used for analysis.

Pupillary function

Responsiveness of the pupils to light was assessed by a single examiner (MB), and scored as normal, weak or unresponsive. The responsiveness of the better eye was used for analysis.

Assessment of endocrine function

All subjects had assessment of endocrine dysfunction based on laboratory testing for growth hormone axis abnormalities, hyperprolactinemia, hypothyroidism, adrenal insufficiency and diabetes insipidus, as reported.⁸ Abnormalities of the growth hormone axis were based on subnormal serum growth hormone responses to glucagon stimulation (growth hormone peak <10 ng/ml). We accepted criteria for central hypothyroidism, central hypoadrenalism and central diabetes insipidus, as determined by the local treating paediatric endocrinologist.

Magnetic resonance imaging

All patients had MRI scans performed. A single neuroradiologist (MN), masked to the patients' clinical data and rest-activity status, reported any malformations based on review of the images, including corpus callosum hypoplasia, absence of the septum pellucidum, pituitary dysgenesis and other major brain malformations.

Rest-activity analysis

Individuals were given Actiwatches (Minimitter, Sunriver, Oregon, USA) to wear on the wrist of their non-dominant hand for 4 weeks. Actiwatches record a digitally integrated measure of gross motor activity that is assessed by an internal accelerometer. The use of Actiwatches to monitor rest-activity patterns and sleep efficiency in children and adults has been validated.⁹ Because sleep-laboratory studies are short term, they are much less useful in assessing circadian rhythmicity than actigraphy, which collects data for extended periods.¹³ An extensive body of data also shows that actigraphy provides data about sleep-wake cycles and sleep disorders.¹³ The manufacturer calibrated the Actiwatches 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. Data were analysed to determine the time of sleep onset and waking. The ratio of activity patterns during the daytime (07:00–21:00) and night-time (21:00–07:00) was also obtained. Circadian period was calculated using chi-squared periodogram analysis to assess periodicity.¹⁴

Sleep efficiency was calculated as the ratio of total sleep time to sleep period.¹⁵ Analyses were performed using Actiware software (Minimitter). Based on Actograms analysis, individuals were classified as being normal (τ 24 h), having free running rhythms (τ >24 h), having fragmented sleep (<85%) or arrhythmic (no discernible rhythmicity). When such criteria are applied to the populations of healthy individuals, including children, 0% of individuals should have free-running rhythms, fragmented sleep or be arrhythmic.^{9 13}

Neurocognitive assessment

Neurocognitive function was assessed using the Battelle Developmental Inventory (BDI), as reported.¹⁶ The BDI consists of parental interview and individual assessment and includes five domains: personal-social, adaptive, motor, communication and cognitive ability.¹⁷ The lowest possible score on the BDI is 65.

Score categories include developmental delay (65–69), borderline (70–79), low average (80–89), average (90–109), high average (110–119), superior (120–129) and very superior (130). Most participants (15/19) underwent developmental assessment the day monitoring of rest-activity patterns began. Of the other four participants, three had developmental assessment less than 1 month before rest-activity monitoring, and one participant had developmental assessment 4 months before rest-activity monitoring. Due to small sample size, participants were categorised either as delayed (65–69) or not delayed (\geq 70) based on their total BDI score.

Statistical methods

Data were collected and analysed using Excel spreadsheets. Sleep data were examined for associations with visual acuity, developmental delay and endocrinopathies. Data are presented as mean (SD). Paired comparisons among groups were made by Student *t* test or the Spearman's rank order test. Multiple comparisons among groups were performed by the Kruskal-Wallis test with Dunn post-test comparisons. Significance was set as $p < 0.05$.

RESULTS

Twenty-three children met criteria for eligibility. Nineteen of the twenty-three individuals who were given the watches wore them for 4 weeks. The characteristics of these children are shown in table 1. Four children either did not wear the watches or returned the devices damaged.

Analysis of expressed rhythmicity revealed normal patterns of activity in 13 (68%) of the children, with distinct periods of rest and activity (figure 1). For the children with normal rhythmicity, the average waking time in the morning was between 06:30 and 08:00. The time when the children went to sleep was between 21:00 and 23:00. Sleep efficiency ranged from 88% to 95%, agreeing with values for control individuals.^{9 18 19} The ratio of daytime to night-time activity bouts was 12.4 (2.7). Period analysis revealed an average period length of 24.01 (0.01) h for this group.

Six children (32%) showed evidence of abnormal activity patterns (figures 1 and 2). Of the six children with abnormal rhythmicity, three had fragmented sleep with sleep efficiency scores that were less than 50% (figure 1). One child had a free-running rest-activity cycle with a short period length of 23.2 h (figure 1). Two children were arrhythmic without day-night distinctions in rest-activity patterns (figure 1). When parameter of vision in the better eye were compared among groups, the children with severe visual impairment were more likely to have abnormal sleep-wake cycles (table 2). None of the children with normal sleep-wake cycles had light perception or less in their better eye, compared with 50% (3/6) of children with abnormal sleep-wake cycles who had light perception only and 17% (1/6) who had no light perception. Alternatively, visual acuity in the better eye was in the best vision category for 60% (8/13) of those with normal sleep-wake cycles, compared to no participants with an abnormal sleep-wake cycle.

Table 1 Characteristics of all children studied

No of patients	19
Age (months)	43 (12.8)
Vision score	2.6 (1.7)
Bilateral ONH	84%
Developmental assessment score	82 (15)

ONH, optic nerve hypoplasia.
Values are mean (SD).

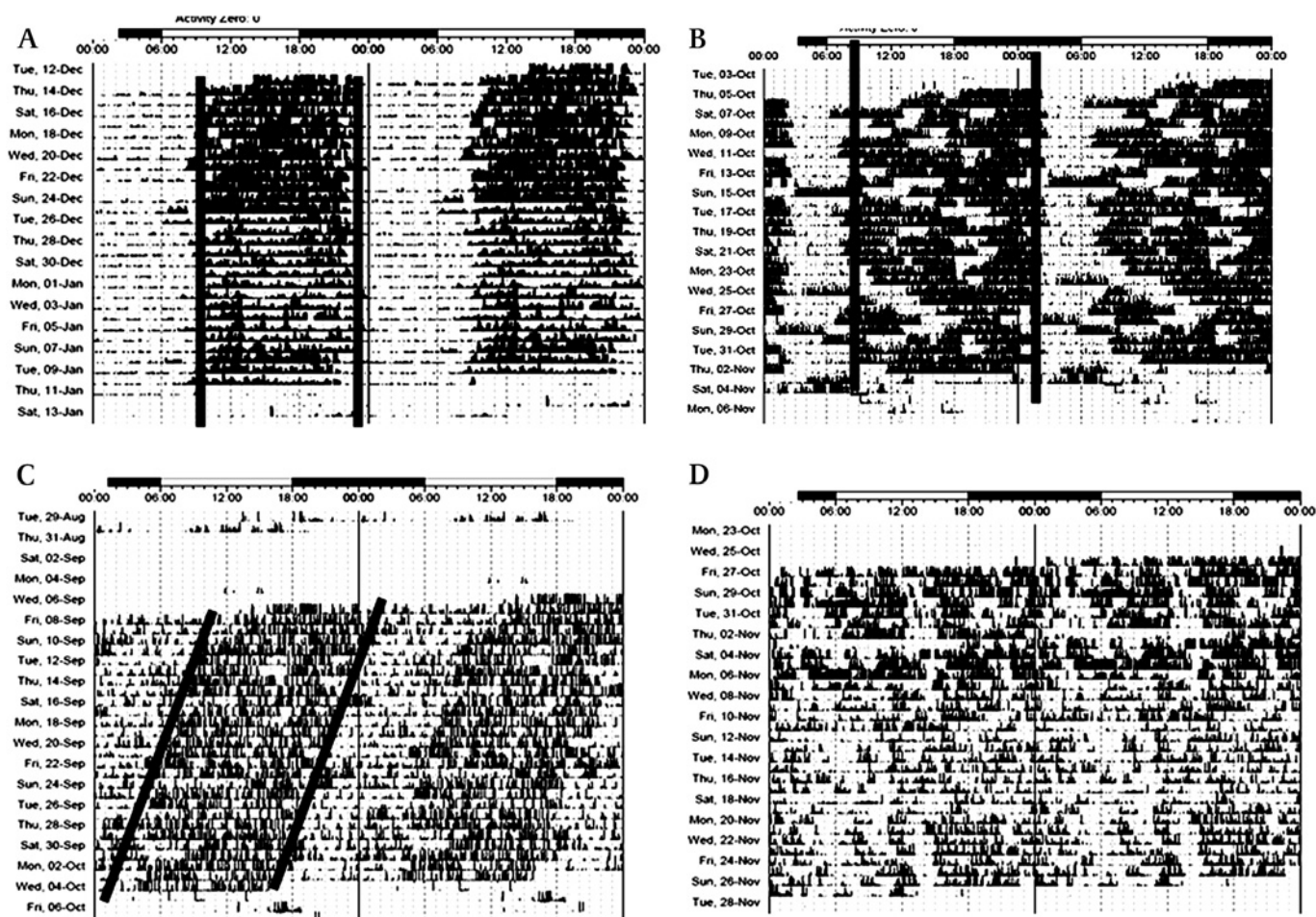


Figure 1 Representative actograms of rest–activity patterns in children with optic nerve hypoplasia. Dark bars represent activity; the same activity scale is used in each plot. The time of day is shown on top. A. Normal. B. Fragmented sleep. C. Free running. D. Arrhythmic. Black lines represent onset and offset of peak period of activity.

When pupillary light responsiveness was examined, 63% of the children had normal pupillary response in at least one eye, 26% had weak pupillary response and 11% were unresponsive in both eyes. Sixteen per cent had one eye with normal response and the other eye with either a weak or unreactive response. Of those children with normal rest–activity patterns, 85% had normal responsiveness in at least one eye, and 0% were unreactive in both eyes (table 2). Of those children with abnormal rest–activity patterns, 17% had normal response (one subject), 50% had weak response and 33% were unreactive ($p=0.0084$ vs normal rest–activity group).

Two of the thirteen children with normal rhythmicity had developmental delay (15%), whereas all six children with abnormal rhythmicity had developmental delay (100%), $p=0.04$ (table 2).

Of the children with normal rhythmicity, growth hormone deficiency was present in 53%, hypothyroidism in 23%, adrenal insufficiency in 30%, and no child had diabetes insipidus (table 3). Of the children with abnormal rhythmicity, growth hormone deficiency was present in 66%, which did not differ statistically from individuals with normal rhythmicity ($p>0.05$ vs normal; table 3). Hypothyroidism was present in 50% of children ($p>0.05$ vs normal; table 3). Adrenal insufficiency was present in 66% of children ($p>0.05$ vs normal). Diabetes insipidus was seen in 33% of children ($p>0.05$ vs normal; table 3).

We also analysed for the presence of multiple hormonal deficiencies. Two or more hormonal deficiencies (growth hormone,

thyroid hormone, adrenal, diabetes insipidus) were present in 30% of children with normal rhythmicity versus 66% of children with abnormal rhythmicity ($p>0.05$). Three or more hormonal deficiencies were present in 7% of children with normal rhythmicity versus 66% of children with abnormal rhythmicity ($p=0.032$).

The corpus callosum was hypoplastic in 30% of children with normal rhythmicity, compared to 66% of children with abnormal rhythmicity ($p>0.05$ vs normal; table 3).

DISCUSSION

Studying children with ONH, we find that abnormal rest–activity rhythmicity is present in approximately 30% of individuals with this condition. The best predictors of abnormal rhythmicity are developmental delay, severe visual impairment with weak pupillary responsiveness and multiple hormonal deficiencies.

In our previous studies of children with anterior hypothalamic lesions due to congenital conditions or brain tumours, we observed that patterns of rest and activity were usually normal.⁹ Of the children with congenital hypopituitarism previously studied, we observed abnormal rest–activity patterns only in those children with ONH (two of four children).⁹ We also previously reported one child with ONH who had arrhythmic behaviour patterns.¹⁰

In the current study, we examined patterns of rest–activity in the 19 children with suitable actigraphy data. We observed that activity patterns were normal in 13 of the 19 individuals. Three

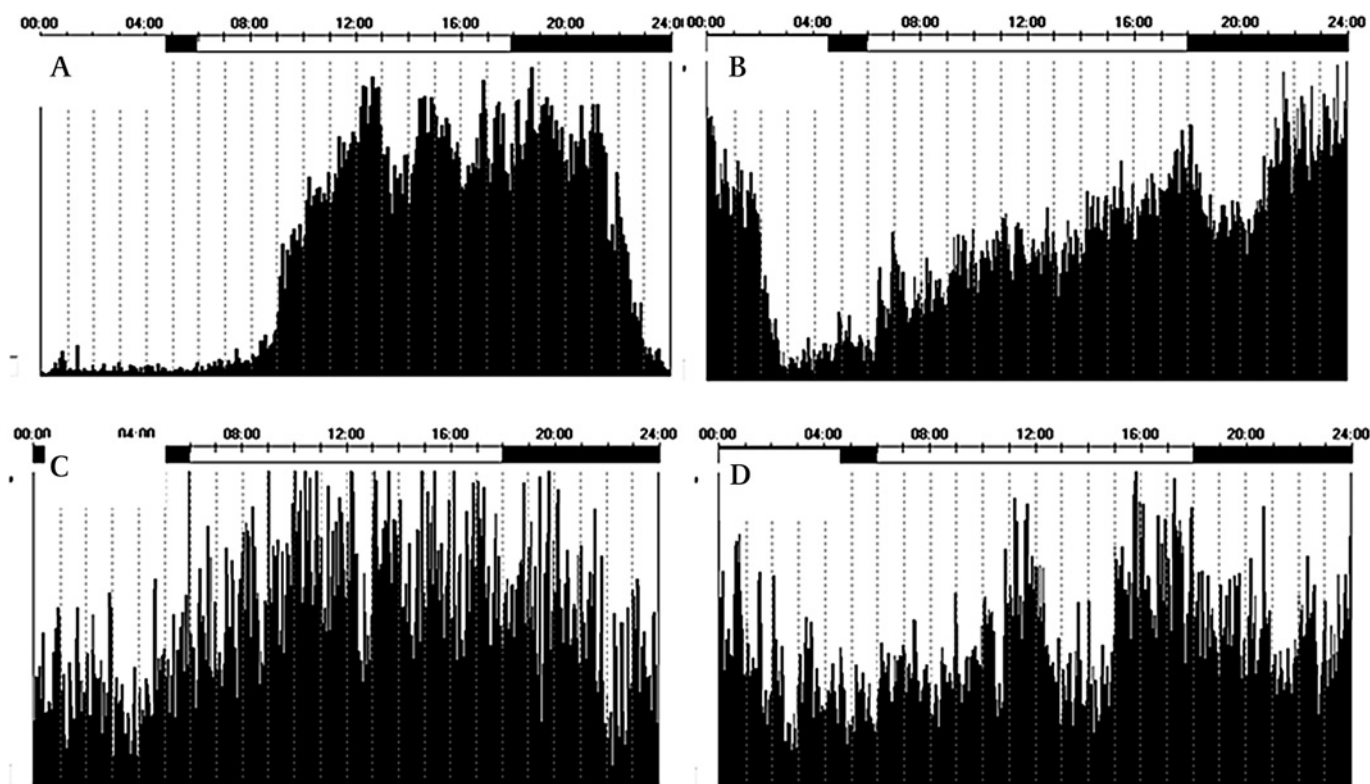


Figure 2 Counts of activity distributed during the 24 h day. A, B, C and D correspond with patients in figure 1.

children had fragmented sleep, one child had free-running rest–activity cycles and two children were arrhythmic. Thus, ONH appears to be associated with a considerable rate of abnormally expressed rhythmicity.

Free-running activity patterns, such as that observed in one child, have been seen in other children and adults with blindness.²⁰ This problem is believed to reflect absent innervation of the SCN by the retina.²⁰ Despite the presence of visual impairment in our cohort, we observed that all but one child had normally entrained circadian phase. These observations suggest that in most children with ONH, there is sufficient innervation of the SCN by the retino-hypothalamic tract to result in entrainment. Alternatively, it is possible that non-photic social cues are helping to entrain these children. The lone child with free-running rhythmicity was visually impaired (category 3 vision), but less severely than the other children with rest–activity pattern irregularities. This child had normal pupillary responses, indicating that free-running activity patterns may be a feature of ONH independent of the residual afferent innervations, although it is

possible that this individual has abnormal retino-hypothalamic tract projections.

Arrhythmicity was seen in two other children, which is indicative of primary circadian pacemaker dysfunction. Because circadian rhythms are generated and regulated by the SCN, which are located in the anterior hypothalamus,^{12–21} it is also possible that some of these children have associated malformations involving the suprachiasmatic nucleus. Yet, at present, we know little about SCN anatomy in children with ONH. We also observed fragmented sleep in three of the children with ONH. This pattern is reflective of disrupted sleep architecture and is characterised by night-time waking.²² Potential causes of this problem can include sleep apnoea or the use of stimulant medications, which were not specifically assessed for in this study.²²

When we looked of risk factors that distinguish ONH children with normal versus abnormal rhythmicity, we found that all children with abnormal rhythmicity were developmentally delayed with severe visual impairment, whereas children who were not developmentally delayed had normal rhythmicity. We also found that whereas pituitary dysfunction was present in children with normal and abnormal rhythmicity, the likelihood of abnormal rhythmicity was greatest in the children with three or more hormonal deficiencies.

It is uncertain whether abnormal rhythmicity contributes to developmental delay in children with ONH, or whether both occur together in children with more severe central nervous system injury. Increasing evidence shows that abnormal patterns of expressed rhythmicity can have profound effects on child physiology, behaviour and interactions with other family members and social contacts.^{23–24} Children with free-running rhythmicity will drift in and out of phase with the normal 24 h light–dark cycle. Children who are arrhythmic will not have consolidated periods of wakefulness and sleep, which can

Table 2 Characteristics of children with ONH with normal versus abnormal rhythmicity

	Normal rest–activity patterns	Abnormal rest–activity patterns	p Value
Number patients	13	6	
Age (months)	44 (11.9)	40 (15.2)	0.45
Vision score	1.7 (1.1)	4.7 (1.0)	0.0067
Bilateral ONH	76%	100%	0.5
Normal pupillary reflex (one eye)	85%	17%	0.0084
Developmental assessment score	89 (12.0)	65	0.0108

ONH, optic nerve hypoplasia.

Values are mean (SD).

Parametric differences were assessed by Student's t test.

Table 3 Characteristics of children with ONH with normal versus abnormal rhythmicity

	Normal rest–activity patterns	Abnormal rest–activity patterns	p Value
No of patients	13	6	
Corpus callosum hypoplasia	30% (4)	66% (4)	0.18
Growth hormone deficiency	53 (7)	66% (4)	0.26
Thyroid hormone deficiency	23% (3)	50% (3)	0.32
Adrenal hormone deficiency	30% (4)	66% (4)	0.18
Diabetes insipidus	0% (0)	33% (2)	0.17
Two or more hormonal deficiencies	30% (4)	66% (4)	0.11
Three hormonal deficiencies	7% (1)	66% (4)	0.03
Developmental delay	15% (2)	100% (6)	0.04

ONH, optic nerve hypoplasia.

Values are mean (SD).

Non-parametric differences were assessed by Kruskal–Wallis test with Dunn post-test comparisons.

disrupt interactions at school and at home. Fragmented sleep will also lead to poor sleep quality.²²

Clinical approaches have been developed to treat circadian system disorders resulting in normalisation of sleep–wake cycles. These interventions can include behavioural approaches and the timed administration of melatonin²⁰ As such, studies are warranted to assess the utility of such approaches in children with ONH.

Overall, we find that children with ONH are at high risk for abnormally expressed circadian rhythmicity, especially when there is developmental delay, severe visual impairment and multiple hormonal deficiencies. Further studies are indicated to help discern potential mechanisms by which rest–activity abnormalities occur in children with this condition and develop appropriate therapeutic approaches for children with circadian system dysfunction.

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Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Yale University and Childrens Hospital of Los Angeles.

Provenance and peer review Not commissioned; externally peer reviewed.

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