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Original Article

Neuronal Ceroid Lipofuscinosis and Associated Sleep Abnormalities

Lenora M. Lehwald MD [a,b,c,d,*], **Rachael Pappa BS** [e], **Sally Steward APN** [f], **Emily de los Reyes MD** [a,b,d]

[a] *The Ohio State University, Columbus, Ohio*
[b] *Department of Pediatrics and Neurology, Columbus, Ohio*
[c] *Department of Sleep Medicine, Columbus, Ohio*
[d] *Nationwide Children's Hospital, Columbus, Ohio*
[e] *Ohio University Heritage College of Osteopathic Medicine, Dublin, Ohio*
[f] *Nationwide Children's Hospital, Department of Neurology, Columbus, Ohio*

ABSTRACT

PURPOSE: The aims of this study were to evaluate sleep difficulties in children with neuronal ceroid lipofuscinosis and to determine the association between the sleep difficulties and the onset of seizures and loss of vision. **METHOD:** We recruited individuals with a confirmed diagnosis of neuronal ceroid lipofuscinosis. We obtained information from the caregiver using the validated Children's Sleep Habits Questionnaire which is a sleep instrument for both behaviorally and medically based problems. Additional information was collected including onset of symptoms, treatment trials, and screen for restless leg syndrome symptoms. **RESULTS:** In our cohort of 54 individuals, 96.3% had sleep scores consistent with a sleep disturbance. Sleep subscale analysis provided additional insight into the characteristics of the sleep disturbance. Fifty two of the 54 patients had at least one abnormal sleep subscale. The onset of sleep disturbance was associated with the onset of both seizures ($\rho = 0.5834$, $P < 0.0001$) and loss of vision ($\rho = 0.3840$, $P = 0.0084$). Restless leg syndrome symptoms were reported in 35.2%. **CONCLUSION:** Children with neuronal ceroid lipofuscinosis have a high burden of sleep disturbances. Using the results of a sleep disturbance screening tool can help to identify the most disturbing symptoms. Targeted treatment of sleep disturbance may improve the quality of life for the patient and family.

Keywords: sleep, neuronal ceroid lipofuscinosis, seizures, vision loss, restless leg syndrome

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Introduction

Neuronal ceroid lipofuscinosis is the most common childhood neurodegenerative disorder. It is characterized by the accumulation of autoflourescent waxy lipopigments in the brain and other tissues along with progressive symptoms including blindness, seizures, ataxia, myoclonus, and loss of developmental milestones or dementia. Sleep disturbance impairs quality of life, cognition, and seizure control in both children and adults.[1] This is the first study including all forms of confirmed neuronal ceroid lipofuscinosis to evaluate the relationship between sleep disturbance and the onset of seizures and loss of vision.

A few studies have confirmed the presence of sleep disorders in individuals with specific neuronal ceroid lipofuscinosis forms.[2] Twelve children with the variant form of late infantile neuronal ceroid lipofuscinosis (CLN5) were studied using a sleep questionnaire to assess sleep disturbances, motor activity monitors and an overnight polysomnogram. These authors found an excess of nocturnal sleep and frequent daytime naps in individuals aged less than 20 years. In older individuals, there were frequent

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* Communications should be addressed to: Dr. Lehwald; Department of Pediatrics and Neurology; The Ohio State University; 700 Children's Drive; Columbus, OH 43205.
E-mail address: lenora.lehwald@nationwidechildrens.org

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shifts of the longest sleep period into daytime and fragmented diurnal sleep. They concluded that progressive disease might damage the internal circadian timing system and impair the ability of the individual with a variant form of late infantile neuronal ceroid lipofuscinosis (CLN5) to use external time cues for synchronization of their sleep and environmental ties.

Using an overnight polysomnogram to evaluate sleep, Kirveskari et al.[3] found the majority of 28 patients with juvenile neuronal ceroid lipofuscinosis (CLN3) had abnormalities. The total sleep time, sleep efficiency, percentages of rapid eye movement, and stage 2 sleep were decreased. These individuals had an increased number of nocturnal awakenings and increased stage 1 sleep. They concluded that in patients with juvenile neuronal ceroid lipofuscinosis, sleep is consistently altered.

Identification of specific neuronal ceroid lipofuscinosis form sleep abnormalities may be helpful to determine the most effective treatment.

Methods

This study was approved by the institutional review board of Nationwide Children's Hospital. We recruited children with a known diagnosis of neuronal ceroid lipofuscinosis. Individuals were recruited at the Nationwide Children's Hospital Batten Disease Center of Excellence and the 2013 and 2014 Batten Disease Support and Research Association annual conferences. Eligible families whose children had died at the time of the study were included. Information was obtained by questionnaire, gathering the following: form of neuronal ceroid lipofuscinosis, presence or absence of blindness, presence or absence of seizures, previous sleep evaluation and/or treatments, screen for sleep disturbance, and symptoms of restless leg syndrome (RLS). Data were evaluated for a correlation among the form of neuronal ceroid lipofuscinosis, timing of sleep difficulties onset, onset of seizures, and loss of vision.

We used a validated caregiver questionnaire to assess for sleep disturbance, the Children's Sleep Habits Questionnaire (CSHQ).[4] The CSHQ is a retrospective sleep screening instrument to consider both behaviorally and medically based sleep problems in school-aged children. The CSHQ is based on common clinical symptom presentations of the most prevalent pediatric *International Classification of Sleep Disorders*[5] diagnoses. It is a well-established sleep screening instrument for identifying sleep problems in children aged four through 12 years.[6] The CSHQ categorizes eight key sleep domains into subscales—bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, night waking, parasomnias, sleep disordered breathing (SDB), and daytime sleepiness. A total sleep disturbance score is calculated from the 33 items which comprise the CSHQ. Items are rated on a three-point scale: "usually" if sleep behavior occurred five to seven times per week, "sometimes" for two to four times per week, and "rarely" for zero to one time per week. High score is indicative of more disturbed sleep. A total sleep disturbance score greater than 41 is sensitive and specific for a sleep disturbance. The CSHQ has been used in studies to evaluate the sleep in children with neurological disorders including autism and Down syndrome.[7,8] The subscale scores for sleep domains have proved useful for both screening purposes and tracking treatment effects.[9] Our cohort includes currently affected children and those who were affected in previous decades. The retrospective CSHQ test allows for collection of this information but comprising a well-matched control group is unattainable. To allow for further subscale analysis, we used the data collected during the original CSHS validation with a control group of 469 school-aged children to compare our study participants. We considered abnormal to be greater than the average control group sample value plus one standard deviation.

Using a separate questionnaire, we also screened for symptoms consistent with RLS, which is a treatable cause of sleep disturbance in children.[10] The diagnosis of RLS is strictly clinical with four essential criteria: (1) uncomfortable sensation or unexplainable urge to move legs or other body part, (2) increasing symptoms with rest or inactivity, (3) a reduction of symptoms with movement, and (4) a circadian enhancement of symptoms in the evening or night. To screen for RLS symptoms, 10 questions were asked to assess the essential criteria and other information which is considered supportive of the diagnosis in children such as family history of RLS.[11] The probable diagnosis of RLS was made when four of the seven questions regarding the symptoms and family history of RLS were positive.

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Statistical analysis

To test whether the patients in our study differ from the control values obtained during the CSHQ validation study (N = 469),[4] we performed independent samples *t* tests. Separate *t* tests were computed for each subscale for the whole sample and within neuronal ceroid lipofuscinosis types 1, 2, and 3. Because the control sample data were from a suburban community school system in Southeastern New England and our patients are from multiple regions of North America and England, it may differ in important respects from the clinical sample used in this study (such as demographics). Therefore it is possible that any differences could be due in part to other, unobserved factors. We also examined differences in the sleep subscales and symptom onset between neuronal ceroid lipofuscinosis types 1, 2, and 3 using one-way ANOVA, with a Tukey adjustment for multiple comparisons. For all tests, we verified that the normality and equality of group variances assumptions were met. Finally, we used Pearson correlation coefficients to examine the relationship between age of sleep disturbance, onset age of seizure, and vision symptom onset.

Results

In total, 64 families were solicited to complete the questionnaire. In nine families, there were two affected children. Six of the children had died before the beginning of the study. A total of 57 questionnaires were returned. Three were excluded from analysis, two due to a lack of confirmed neuronal ceroid lipofuscinosis diagnosis and the other due to incompleteness.

In our cohort, all but two of the 54 individuals (96.3%) had a total sleep disturbance score on the CSHQ of greater than 41. The average total sleep disturbance score for all individuals = 71.8, standard deviation = 13.3, range = 24 to 96. Ninety six percent of the patients had at least one sleep subscale which was abnormal. When the entire cohort is considered, the age of onset of sleep disturbance is moderately associated with age of onset of both seizure ($\rho = 0.5834$, $P < 0.001$) and vision ($\rho = 0.3840$, $P = 0.008$) symptoms, with later onset of sleep disturbance tending to occur alongside later onset of vision and seizure symptoms. We found no statistically significant differences between neuronal ceroid lipofuscinosis forms for any of the sleep difficulty subscales. However, age of symptom onset differs between groups for every symptom. More specifically, the age of symptom onset for CLN3 is older than for CLN1 or CLN2. In addition, on average, the age of symptom onset is older among CLN2 individuals compared with CLN1 individuals, but this difference was not statistically significant.

Seven of the eight sleep subscale variables were statistically significant when compared control group of the initial CSHQ validation: bedtime resistance ($P = 0.012$), sleep onset delay ($P < 0.001$), sleep duration ($P < 0.001$), night wakings ($P < 0.001$), parasomnias ($P < 0.001$), SDB ($P = 0.009$), and daytime sleepiness ($P < 0.001$; Fig 1).