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# Prevalence of Sleep Disturbances in Children With Neurofibromatosis Type 1

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**Abstract**

Children with neurodevelopmental disorders are at increased risk for sleep issues, which affect quality of life, cognitive function, and behavior. To determine the prevalence of sleep problems in children with the common neurodevelopmental disorder neurofibromatosis type 1, a cross-sectional study was performed on 129 affected subjects and 89 unaffected siblings, age 2 to 17 years, using the Sleep Disturbance Scale for Children questionnaire. Children with neurofibromatosis type 1 were significantly more likely to have disturbances in initiating and maintaining sleep, arousal, sleep-wake transition, and hyperhidrosis, but not problems with abnormal sleep breathing, or excessive somnolence. Although the overall sleep scores were higher in children with neurofibromatosis type 1, this was not related to a coexisting attention deficit disorder, cognitive impairment, or stimulant medication use. Collectively, these results demonstrate that children with neurofibromatosis type 1 are more likely to have sleep disturbances, and support the use of appropriate interventions for this at-risk population.

**Keywords**

NF1, sleep disturbances, neurocutaneous disorders, brain tumor

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Neurofibromatosis type 1 is one of the most common autosomal dominant tumor predisposition syndromes in which affected children develop nervous system abnormalities.[1] In addition to an increased risk for developing benign and malignant tumors of the central and peripheral nervous system, individuals with neurofibromatosis type 1, especially young children, are prone to a wide range of cognitive and behavioral issues.[2,3] Whereas approximately 8.4% of children in the general population meet criteria for attention deficit-hyperactivity disorder (ADHD),[4] approximately 40%-50% of children with neurofibromatosis type 1 are diagnosed with attention deficit-hyperactivity disorder. Of these children, 60% show impairments in sustained attention, divided attention, and response inhibition.[5-7]

Moreover, learning disabilities, as defined by discrepancies in Intelligence Quotient and achievement, are present in about 20% of children with neurofibromatosis type 1,[5] compared to 8% in the general population.[8] A left-shift in Intelligence Quotients has been reported for children with neurofibromatosis type 1, with 20% of children with neurofibromatosis type 1 having an Intelligence Quotient score that falls 1 to 2 standard deviations below those of their unaffected siblings.[5] School-age children with neurofibromatosis type 1 have been noted to have more extensive academic and cognitive delays relative to younger children with neurofibromatosis type 1, specifically in math, reading, gross motor, fine motor, and self-help development.[9]

An important contributing factor to cognitive and behavior deficits in children is the presence of sleep disturbances.[10,11] In this regard, children with sleep disturbances frequently score significantly lower on tests of overall intelligence and some aspects of executive function.[12,13] Moreover, some children with disordered sleep exhibit hyperactivity and depression as well as reduced social competency (internalizing and externalizing behavior problems).[14]

Only 1 prior study has assessed sleep issues in children with neurofibromatosis type 1. In this study, children with neurofibromatosis type 1 had higher rates of parasomnias (sleepwalking and night terrors), which correlated with conduct problems,

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**Table 1.** Sleep Disturbances in Children With Neurofibromatosis Type 1 and Unaffected Siblings.

| Sleep issues | Children with neurofibromatosis type 1 (Mean ± SD) | Unaffected (mean ± SD) | $P^a$ | $P^b$ |
|---|---|---|---|---|
| Total | 43.49 ± 13.38 | 38.71 ± 9.91 | <.001 | <.001 |
| Initiating | 14.16 ± 5.65 | 12.37 ± 4.71 | .006 | .005 |
| Breathing | 4.49 ± 1.93 | 4.10 ± 1.63 | .119 | .097 |
| Arousal | 3.52 ± 0.99 | 3.82 ± 1.26 | .041 | .021 |
| Transition | 10.14 ± 4.13 | 8.78 ± 3.09 | .002 | .002 |
| Somnolence | 8.03 ± 3.38 | 7.42 ± 2.83 | .134 | .059 |
| Hyperhidrosis | 3.20 ± 2.01 | 2.35 ± 0.91 | <.001 | <.001 |
| Average hours of sleep | 8.74 ± 1.37 | 9.07 ± 1.35 | .044 | .006 |
| Time to fall sleep | 31.48 ± 35.67 | 21.84 ± 16.48 | .009 | .011 |
| No. of awakenings/night | 0.85 ± 1.19 | 0.55 ± 0.74 | .024 | .024 |
| No. of daily naps | 2.18 ± 1.42 | 2.17 ± 1.48 | .964 | .854 |

[a] Unadjusted *P* values.
[b] *P* values after adjusting age and gender.

hyperactivity, and emotional problems.[15] However, the prevalence of sleep disturbances, spectrum of sleep abnormalities, and associated features has not been fully examined in this population. The purpose of this study was to address these issues in children with neurofibromatosis type 1.

## Methods

Parents of children with neurofibromatosis type 1, age 2 to 17 years, cared for in the Neurofibromatosis Clinical Program at Saint Louis Children's Hospital and Washington University Neurofibromatosis Center completed the Sleep Disturbance Scale for Children questionnaire. The Sleep Disturbance Scale for Children is a validated questionnaire for which a total sleep disturbances score as well as subscores for disorders of initiating and maintaining sleep, sleep breathing disorders, disorders of arousal, sleep-wake transition disorders, disorders of excessive somnolence, and sleep hyperhidrosis can be calculated.[16] On the Sleep Disturbance Scale for Children questionnaire, disorders of arousal include sleepwalking, night terrors, and nightmares, whereas sleep-wake transition disorders include hypnic jerks, rhythmic movements, vivid dreams, leg jerking while asleep, sleep-talking, and bruxism.[16] Parents also completed the Sleep Disturbance Scale for Children questionnaire for unaffected siblings of children with neurofibromatosis type 1, age 2 to 17 years. Parents were asked questions addressing the pediatric criteria for restless legs syndrome diagnosis.[17]

Inclusion criteria for the subjects with neurofibromatosis type 1 required that children were between the ages of 2 and 17 years with a diagnosis of neurofibromatosis type 1 established using National Institutes of Health Consensus Development Conference diagnostic criteria.[18] Exclusion criteria included a diagnosis of neurofibromatosis type 2, age less than 2 years or greater than 17 years, and children who were wards of the state.

A control group was also recruited, consisting of unaffected siblings of children with neurofibromatosis type 1 who were between the ages of 2 and 17 years and slept in a different bedroom separate from their siblings with neurofibromatosis type 1. Control group exclusion criteria included known or suspected neurofibromatosis type 1 or neurofibromatosis type 2, sleeping in the same bedroom as their siblings with neurofibromatosis type 1, ages less than 2 years or greater than 17 years, and children who were wards of the state. This study was performed under an active human studies protocol approved by the Washington University institutional review board and appropriate informed consents were obtained.

The Sleep Disturbance Scale for Children questionnaire scores (overall and subscores) and the sleep characteristics (average hours of sleep, time to fall asleep, number of awakenings per night, and number of daily naps) were summarized by means and standard deviations in children with neurofibromatosis type 1 and unaffected siblings. The differences between subjects with neurofibromatosis type 1 and unaffected siblings were compared using a generalized estimating equation to account for potential correlations among children from the same family. Age and gender were further included in the model to adjust for their potential confounding effects. Regression analysis was performed to assess which factors had significant associations with the sleep score in children with neurofibromatosis type 1. All the above tests were 2-sided and a *P*-value of .05 or less was taken to indicate statistical significance. The statistical analysis was performed using Statistical Analysis Software® (SAS Institutes, Cary, NC).

## Results

A total of 218 children were enrolled, including 129 children with neurofibromatosis type 1 (64 males, 65 females) and 89 siblings of children with neurofibromatosis type 1 (50 males, 39 females) from April 2010 to August 2012. The mean age for children with neurofibromatosis type 1 was 8.58 years (standard deviation 4.18, minimum age 2 years, maximum age 17 years), whereas the mean age for siblings of children with neurofibromatosis type 1 was 9.24 years (standard deviation 4.40, minimum age 2 years, maximum age 17 years).

Compared to their unaffected siblings, children with neurofibromatosis type 1 were significantly more likely to exhibit sleep disturbances (Table 1). Of note, the overall sleep score was higher in children with neurofibromatosis type 1 compared to their unaffected siblings (neurofibromatosis type 1 subject mean score = 43.49, sibling mean score = 38.71; $P < .001$) (Table 1). More than half (53.5%, 68/127) of children with neurofibromatosis type 1 had abnormal sleep scores (39 or higher),[14] whereas 40.5% (36/89) of unaffected siblings had abnormal sleep scores ($P = .048$).

**Table 2.** Somnolence Disorders Score.

| | Children with neurofibromatosis type 1 | | Unaffected children | | |
|---|---|---|---|---|---|
| Hours of sleep | N | Mean ± SD | N | Mean ± SD | $P^a$ |
| ≤6 | 7 | 9.86 ± 4.53 | 5 | 12 ± 5.39 | .305 |
| 7-8 | 50 | 8.92 ± 3.72 | 29 | 7.07 ± 1.94 | .006 |
| 9-10 | 62 | 7.35 ± 2.94 | 42 | 6.69 ± 1.96 | .079 |
| >10 | 10 | 6.50 ± 1.65 | 13 | 8.77 ± 3.77 | .152 |

Abbreviation: SD, standard deviation.
[a] *P* values after adjusting age and gender.

**Table 3.** Mean Total Sleep Score by Gender and Age.

| | Children with neurofibromatosis type 1 | | Unaffected children | | |
|---|---|---|---|---|---|
| Characteristic | N | Mean ± SD | N | Mean ± SD | *P* |
| Gender | | | | | |
| Girls | 65 | 41.53 ± 10.85 | 39 | 37.50 ± 8.67 | .024 |
| Boys | 64 | 45.54 ± 15.42 | 50 | 39.67 ± 10.77 | .021 |
| Age (y) | | | | | |
| 2-4 | 26 | 44.96 ± 12.51 | 13 | 39.50 ± 9.50 | .138 |
| 5-9 | 53 | 42.90 ± 13.36 | 37 | 38.75 ± 9.47 | .055 |
| 10-12 | 24 | 45.00 ± 14.50 | 17 | 39.19 ± 12.78 | .202 |
| 13-17 | 26 | 41.76 ± 13.75 | 22 | 37.86 ± 9.07 | .263 |

Abbreviation: SD, standard deviation.

Specifically, children with neurofibromatosis type 1 exhibited a higher frequency of symptoms indicating abnormalities in initiating and maintaining sleep (neurofibromatosis type 1 subject mean score = 14.16, sibling mean score = 12.37; $P = .006$), sleep-wake transition (neurofibromatosis type 1 subject mean score = 10.14, sibling mean score = 8.78; $P = .002$), and hyperhidrosis (neurofibromatosis type 1 subject score = 3.20, sibling score = 2.35; $P < .001$) but were not more likely to have symptoms indicating problems with sleep breathing (neurofibromatosis type 1 subject mean score = 4.49, sibling mean score = 4.10; $P = .119$) or excessive somnolence (neurofibromatosis type 1 subject mean score = 8.03, sibling mean score = 7.42; $P = .134$). However, children with NF1 exhibited a lower frequency of disturbances in arousal compared to their unaffected siblings (NF1 mean score 3.52, sibling mean score 3.82, $P = 0.041$). In addition, subjects with breathing disturbances were not more likely to exhibit hyperhidrosis. When stratified for nightly hours of sleep obtained, scores indicating excessive somnolence were higher in children with neurofibromatosis type 1 compared to their unaffected siblings if the most typical hours of sleep were obtained (7-8 hours and 9-10 hours; Table 2). The differences in somnolence subscores were significant for 7 to 8 hours of sleep (neurofibromatosis type 1 subject mean score = 8.92, sibling mean score = 7.07; $P = .006$) and marginally significant for 9 to 10 hours of sleep (neurofibromatosis type 1 subject mean score = 7.35, sibling mean score = 6.69; $P = .079$) but not significant if other amounts of sleep were obtained nightly. The conclusions regarding the subscores and total scores in subjects with neurofibromatosis type 1 and their unaffected siblings remained the same after adjusting for age and gender.

The mean total sleep scores by gender and age are shown in Table 3. The differences in mean total sleep scores between children with neurofibromatosis type 1 and unaffected siblings were significant in both girls ($P = .024$) and boys ($P = .021$). Boys with neurofibromatosis type 1 had a higher mean total sleep score than girls with neurofibromatosis type 1, but the difference was not significant (boys: mean = 45.54, standard deviation = 15.42; girls: mean = 41.53, standard deviation = 10.85; $P = .332$), and differences in subscores between boys and girls with neurofibromatosis type 1 were not significant. The mean total sleep scores by age groups in subjects with neurofibromatosis type 1 and unaffected siblings are shown in Table 3 for ages 2 to 4 years, 5 to 9 years, 10 to 12 years, and 13 to 17 years. Although the mean total sleep scores were consistently higher in children with neurofibromatosis type 1 than unaffected siblings in all age groups, none of the differences were statistically significant, possibly because of relatively small sample sizes. Interestingly, there was a trend toward significance in the 5- to 9-year-old age group ($P = .055$). However, when only mean total sleep scores of children with neurofibromatosis type 1 among age groups were compared, there were no significant differences ($P = .777$).

Children with neurofibromatosis type 1 had a more disrupted sleep schedule than their unaffected siblings, with several significant differences. Children with neurofibromatosis type 1 had reduced mean nightly sleep durations (neurofibromatosis type 1 subject mean time =8.74 hours, sibling mean time = 9.07 hours; $P = .044$), longer mean sleep onset latency (neurofibromatosis type 1 subject mean time = 31.48 minutes, sibling mean time = 21.84 minutes; $P = .009$), and a greater mean number of awakenings per night (neurofibromatosis type 1 subject mean awakenings = 0.85, sibling mean awakenings = 0.55; $P = .024$).

Diagnoses of attention deficit disorder, cognitive impairment, or stimulant medication use did not significantly affect the overall sleep scores in children with neurofibromatosis type 1 (Table 4). However, other medications and coexisting medical conditions can also affect sleep. In this regard, 7 of the 67 children with neurofibromatosis type 1 and sleep disturbances had allergies and were prescribed medications for this condition (cetirizine, fexofenadine, mometasone furoate, loratadine). Additionally, 4 children with neurofibromatosis type 1 and sleep problems had asthma and were taking medications (albuterol, fluticasone/salmeterol, montelukast). It should be noted that the nature and severity of the asthma or allergies (eg, exercise-induced, seasonal) as well as the frequency and specific formulations (eg, "non-drowsy" preparations) of the prescribed medications could not be accurately assessed in these children. Finally, birth order can contribute to the frequency of sleep problems. However, the distribution of birth order in children with neurofibromatosis type 1 and sleep disturbances relative to those children with neurofibromatosis type 1 and no sleep problems was similar (data not shown).

**Table 4.** Correlation Between Clinical Features and Mean Total Sleep Score in Children With Neurofibromatosis Type 1.

| Neurofibromatosis type 1–associated feature | Children with the neurofibromatosis type 1–associated feature | | Children without the neurofibromatosis type 1–associated feature | | *P* |
|---|---|---|---|---|---|
| | N | Mean ± SD | N | Mean ± SD | |
| ADHD | 22 | 44.90 ± 13.42 | 104 | 43.54 ± 13.46 | .657 |
| Taking stimulant | 17 | 45.38 ± 13.76 | 108 | 43.66 ± 13.41 | .635 |
| IEP | 19 | 49.11 ± 15.52 | 105 | 42.72 ± 12.84 | .107 |
| Cognitive impairment | 61 | 46.09 ± 14.26 | 64 | 41.62 ± 12.41 | .075 |
| Optic pathway glioma | 21 | 48.52 ± 12.97 | 104 | 42.78 ± 13.41 | .055 |
| Other brain tumor | 12 | 41.58 ± 10.97 | 113 | 44.02 ± 13.67 | .618 |

Abbreviations: ADHD, attention-deficit hyperactivity disorder; IEP, individualized educational plan.

Interestingly, there was a trend toward significance in the association between the presence of a coexisting optic pathway glioma and the total sleep score ($P = .055$). The mean total sleep score did not significantly change with the location of the tumor along the optic pathway when gliomas along the optic nerve, optic chiasm, and optic tract were compared. Only 1 child with an optic pathway glioma had hypothalamic involvement, and 7 subjects had optic chiasm involvement. No child had surgery for an optic pathway glioma. The association between the presence of cognitive impairment and the total sleep score was also marginally significant, and subjects with cognitive impairment had a higher mean total sleep score (46.1 vs 41.6; $P = .075$). Restless legs syndrome was diagnosed in 1 child with neurofibromatosis type 1 and in 1 unrelated unaffected sibling.[15]

## Discussion

Children with neurodevelopmental disorders have a high prevalence of sleep disturbances, with estimates of prevalence ranging from 13% to 86%,[19] compared to 11% to 37% reported for children with typical development.[20,21] Addressing sleep issues is particularly important in children with neurodevelopmental disorders because of the influence of sleep issues on other spheres of functioning, including learning, behavior, and mental health. Sleep disturbances in the pediatric population dramatically impair school performance, memory, and cognition.[22-26] In this regard, children with sleep-disordered breathing are significantly more likely to exhibit hyperactivity, inattention, and aggressiveness relative to their unaffected counterparts.[27] In addition to affecting childhood functioning, childhood insomnia can predispose individuals to develop depression and anxiety later in life.[28] Fortunately, treatment of the underlying sleep abnormalities has been shown to improve the quality of life and behavior in children with obstructive sleep apnea.[29]

Given the high incidence of cognitive and behavioral problems in children with neurofibromatosis type 1, we hypothesized that 1 etiologic factor is disturbed sleep. In this report, we show that children with neurofibromatosis type 1 were significantly more likely to have symptoms indicating abnormalities in initiating and maintaining sleep, sleep-wake transition, and hyperhidrosis and were more likely to have a higher total sleep score. Insomnia and sleep-wake transition disorders can be associated with sleep disruption and sleepiness,[30-31] potentially affecting daytime functioning. The presence of hyperhidrosis is also suggestive of poor-quality sleep. In a study of 6381 children, 11.7% had weekly night sweats, and these children were significantly more likely than children without night sweats to have allergic rhinitis, tonsillitis, and symptoms suggestive of obstructive sleep apnea, insomnia, and parasomnias.[32] In an adult study of 363 patients, night sweats were associated with sleepiness, legs jerking during sleep, and awakening with pain in the night.[33] Night sweats could also be found in panic attacks,[34] arousal responses during nightmares, or autonomic dysfunction from sympathetic overstimulation of the sweat glands.[32]

Although sleep disorders can affect cognitive functioning, our study did not show statistical differences in the mean total sleep scores in patients with neurofibromatosis type 1 relative to those without cognitive impairments or those requiring an individualized educational plan. However, subjects with neurofibromatosis type 1 and cognitive impairment or requiring an individualized educational plan had higher mean total sleep scores than subjects with neurofibromatosis type 1 without known cognitive impairment or an individualized educational plan. Future larger studies focused on this association will be required to confirm these suggestive differences.

In all age groups, children with neurofibromatosis type 1 had higher mean total sleep scores, with the difference approaching significance in the 5-to 9-year-old age group. Middle-childhood-age subjects with neurofibromatosis type 1 could be in a transition phase, perhaps exhibiting vulnerability to both sleep disorders more prevalent in early childhood (bedtime resistance, parasomnias, and night wakings) and sleep disorders more prevalent in adolescence, as reported in a study of children with autism (delayed sleep onset, shorter sleep duration, and daytime sleepiness).[35] Children with neurofibromatosis type 1 also had more disrupted sleep relative to their unaffected siblings, with reduced mean nightly sleep durations, longer mean sleep-onset latencies, and greater mean numbers of awakenings per night. Short sleep duration has been associated with worse school performance, sleepiness, and depression.[36] In contrast, coexisting attention deficit disorder, cognitive impairment, or stimulant medication use did not significantly affect the overall sleep score

among children with neurofibromatosis type 1, although there was a trend toward significance in association with optic pathway glioma.

To our knowledge, this is the first and largest report to characterize sleep disturbances in children with neurofibromatosis type 1, and the first to assess for associations between specific clinical characteristics in children with neurofibromatosis type 1 and sleep disturbance scores. The use of unaffected siblings as control group is a major advantage of the current study, because it accounts for unobserved family-based confounding factors. The mean total sleep score of our control group (38.71) was relatively similar to the mean sleep score of the validation study for the Sleep Disturbance Scale for Children questionnaire. In the validation study, the mean total sleep score for control subjects was 35.05 (standard deviation = 7.70) and the mean total score in children with sleep disorders was 54.87 (standard deviation = 12.49) with a cut-off score for abnormality of 39 with sensitivity of 0.89 and specificity of 0.74.[16]

There are limitations to this study, including the limitations associated with the use of parental questionnaires for assessing sleep characteristics. For example, in a study of adolescents using sleep diary estimates, actigraphic estimates of wake after sleep onset were substantially greater and total sleep times were substantially shorter than reported.[37] In addition, future prospective studies will be required to define the potential contributions of other medications, coexisting medical conditions, and parental occupation (eg, night shift workers) on sleep in children with neurofibromatosis type 1.

The findings described in this study raise many important questions worthy of further pursuit. Studies are currently planned to further characterize sleep issues in children with neurofibromatosis type 1 using additional objective methods of assessment, including actigraphy and polysomnography. Exciting studies using *Drosophila Neurofibromatosis type 1* mutants revealed increased frequencies of arrhythmic light-dark cycles.[38] Future studies in which sleep schedule data and actigraphy measurements are collected will enable a more critical assessment of circadian rhythm disorders in this population. Similarly, it will be critical to determine whether correcting sleep disturbances in children with neurofibromatosis type 1 will have a positive impact on their scholastic performance, learning, memory, and attention system function.

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## Author Contributions

AKL performed the data analysis and wrote the first drafts of the manuscript. FG performed the statistical analyses. AV and AKL created the tables. FG and AKL edited the tables. AV and CC collected the data. JL collected and compiled the data. KAY and SPD provided expert input. DHG performed the final editing of the manuscript.

## Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Duntley has a consulting relationship with UCB, Inc, and is participating in a multicenter trial involving Rotigotine for restless leg syndrome. Dr. Duntley has a consulting relationship with Jazz Pharmaceuticals. The other authors have no financial conflicts of interest to report.

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## Ethical Approval

This study was conducted under an approved Human Studies Protocol at the Washington University School of Medicine (#201103204).

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