Published in final edited form as:

J Child Neurol. 2013 November ; 28(11): 1400–1405. doi:10.1177/0883073813500849.

Prevalence of Sleep Disturbances in Children with Neurofibromatosis Type 1

Amy K. Licis, MD¹, Alicia Vallorani, BA¹, Feng Gao, MD, PhD², Cynthia Chen, BA¹, Jason Lenox, MS¹, Kelvin A. Yamada, MD¹, Stephen P. Duntley, MD¹, and David H. Gutmann, MD, PhD¹

¹Department of Neurology, Washington University School of Medicine, St. Louis, MO 63110, USA

²Division of Biostatistics, Washington University School of Medicine, St. Louis, MO 63110, USA

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 2-17 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. While the overall sleep scores were higher in children with neurofibromatosis type 1, this was not related to a co-existing 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

Introduction

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 of 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,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}

Address correspondence to: David H. Gutmann, MD, PhD, Department of Neurology, Washington University School of Medicine, Box 8111, 660 S. Euclid Avenue, St. Louis MO 63110. Phone (314-362-7379); FAX (314-362-2388); (gutmann@neuro.wustl.edu).

Author Contributions: A.K.L. performed the data analysis and wrote the first drafts of the manuscript, F.G. performed the statistical analyses, A.V. and A.K.L. created the tables, F.G. and A. K. L. edited the tables, A.V., and C.C. collected the data, J.L. collected and compiled the data, K.A.Y. and S.P. D. provided expert input, and D.H.G. performed the final editing of the manuscript.

Moreover, learning disabilities, as defined by discrepancies in IQ and achievement, are present in about 20% of children with Neurofibromatosis type 1,⁵ compared to 8% in general population.⁸ A left-shift in IQs has been reported for children with Neurofibromatosis type 1, with 20% of children with Neurofibromatosis type 1 having an IQ 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 one 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, 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 2-17 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 2-17 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 2-17 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 two-sided and a p-value of 0.05 or less was taken to indicate statistical significance. The statistical analysis was performed using Statistical Analysis Software® (SAS Institutes, Cary, NC).

Results

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; $p < 0.001$) (**Table 1**). 53.5% (68/127) of children with Neurofibromatosis type 1 had abnormal sleep scores (39 or higher),¹⁴ while 40.5% (36/89) of unaffected siblings had abnormal sleep scores ($p = 0.048$).

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; $p = 0.006$), sleep-wake transition (Neurofibromatosis type 1 subject mean score = 10.14, sibling mean score = 8.78; $p = 0.002$), arousal (Neurofibromatosis type 1 subject mean score = 3.52, sibling mean score = 3.82; $p = 0.041$), and hyperhidrosis (Neurofibromatosis type 1 subject score = 3.20, sibling score = 2.35; $p < 0.001$), 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; $p = 0.119$) or excessive somnolence (Neurofibromatosis type 1 subject mean score = 8.03, sibling mean score = 7.42; $p = 0.134$). 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 7-8 hours of sleep (Neurofibromatosis type 1 subject mean score = 8.92, sibling mean score = 7.07; $p = 0.006$) and marginally significant for 9-10 hours of sleep (Neurofibromatosis type 1 subject mean score = 7.35, sibling mean score = 6.69; $p = 0.079$), 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 ($p=0.024$) and boys ($p=0.021$). 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 $45.54 \pm \text{S.D.}15.42$, girls 41.53 ± 10.85 ; $p=0.332$), 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 2-4 years, 5-9 years, 10-12 years, and 13-17 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 due to relatively small sample sizes. Interestingly, there was a trend towards significance in the 5-9 year old age group ($p=0.055$). However, when only mean total sleep scores of children with Neurofibromatosis type 1 among age groups were compared, there were no significant differences ($p=0.777$).

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; $p=0.044$), longer mean sleep onset latency (Neurofibromatosis type 1 subject mean time = 31.48 minutes, sibling mean time = 21.84 minutes; $p=0.009$), and a greater mean number of awakenings per night (Neurofibromatosis type 1 subject mean awakenings = 0.85, sibling mean awakenings = 0.55; $p=0.024$).

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 co-existing medical conditions can also affect sleep. In this regard, seven of the 67 children with NF1 and sleep disturbances had allergies and were prescribed medications for this condition (Cetirizine, Fexofenadine, Mometasone Furoate, Loratadine). Additionally, four children with NF1 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 (e.g., exercise-induced, seasonal) as well as the frequency and specific formulations (e.g., “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 NF1 and sleep disturbances relative to those children with NF1 and no sleep problems was similar (data not shown).

Interestingly, there was a trend towards significance in the association between the presence of a co-existing optic pathway glioma and the total sleep score ($P=0.055$). 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 one child with an optic pathway glioma had hypothalamic involvement, and seven 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; $p=0.075$). Restless legs syndrome was diagnosed in one child with Neurofibromatosis type 1 and in one 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 11-37% reported for children with typical development.^{20,21} Addressing sleep issues is particularly important in children with neurodevelopmental disorders due to 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 may 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 one 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 may 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 may 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 impact on 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 5-9 year old age group. Middle childhood age subjects with Neurofibromatosis type 1 may 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, co-existing 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 towards 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, co-existing medical conditions, and parental occupation (e.g., night shift workers) on sleep in children with NF1.

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.

Acknowledgments

We thank Anne C. Albers, PNP, Vicki Kuchnicki, and Elaine Most for their assistance during the execution of this project. A.K.L. was supported by the Neurological Sciences Academic Development Award (K12 NS001690) and the Washington University Institute of Clinical and Translational Sciences grant (UL1 TR000448; National Center for Advancing Translational Sciences). The content of this report is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Dr. Bradley Evanoff is the PI for the Clinical and Translational Science Award (CTSA) that supports all ICTS and CRTC activities. The authors also wish to acknowledge the support of the Biostatistics Core, Siteman Comprehensive Cancer Center and a National Cancer Institute Cancer Center Support Grant (P30 CA091842).

Financial Disclosures and Funding: Dr. Duntley has a consulting relationship with UCB, Inc., and is participating in a multi-center 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. There was no funding for this study.

Ethical Approval: This study was conducted under an approved Human Studies Protocol at the Washington University School of Medicine.

References

1. Friedman, JM. Neurofibromatosis : phenotype, natural history, and pathogenesis. Johns Hopkins University Press; Baltimore: 1999.

2. Gutmann DH, Aylsworth A, Carey JC, et al. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. *JAMA*. 1997; 278:51–7. [PubMed: 9207339]
3. North KN, Riccardi V, Samango-Sprouse C, et al. Cognitive function and academic performance in neurofibromatosis 1: consensus statement from the NF1 Cognitive Disorders Task Force. *Neurology*. 1997; 48:1121–7. [PubMed: 9109916]
4. Pastor PN, Reuben CA. Diagnosed attention deficit hyperactivity disorder and learning disability: United States, 2004–2006. *Vital Health Stat*. 2008; 10:1–14.
5. Hyman SL, Shores A, North KN. The nature and frequency of cognitive deficits in children with neurofibromatosis type 1. *Neurology*. 2005; 65:1037–1044. [PubMed: 16217056]
6. Eliason MJ. Neurofibromatosis: Implications for learning and behaviour. *J Dev Behav Pediatr*. 1986; 7:175–179. [PubMed: 3088045]
7. Isenberg JC, Templer A, Gao F, Titus JB, Gutmann DH. Attention skills in children with neurofibromatosis type 1. *J Child Neurol*. 2013; 28:45–9. [PubMed: 22496119]
8. Boyle CA, Boulet S, Schieve LA, et al. Trends in the Prevalence of Developmental Disabilities in US Children, 1997–2008. *Pediatrics*. 2011; 127:1034–1042. [PubMed: 21606152]
9. Wessel LE, Gao F, Gutmann DH, Dunn CM. Longitudinal Analysis of Developmental Delays in Children With Neurofibromatosis Type 1. *J Child Neurol*. Oct 30.2012 Epub.
10. Blunden S, Lushington K, Kennedy D. Cognitive and behavioural performance in children with sleep-related obstructive breathing disorders. *Sleep Med. Rev*. 2001; 5:447–461. [PubMed: 12531153]
11. Beebe DW. Cognitive, behavioral, and functional consequences of inadequate sleep in children and adolescents. *Pediatr. Clin. North Am*. 2011; 58:649–665. [PubMed: 21600347]
12. Bourke RS, Anderson V, Yang JS, et al. Cognitive and academic functions are impaired in children with all severities of sleep-disordered breathing. *Sleep Med*. 2011; 12:489–496. [PubMed: 21493135]
13. Blunden S, Lushington K, Lorenzen B, Martin J, Kennedy D. Neuropsychological and psychosocial function in children with a history of snoring or behavioral sleep problems. *J Pediatr*. 2005; 146:780–6. [PubMed: 15973318]
14. Bourke R, Anderson V, Yang JS, et al. Neurobehavioral function is impaired in children with all severities of sleep disordered breathing. *Sleep Med*. 2011; 12:222–9. [PubMed: 21324739]
15. Johnson H, Wiggs L, Stores G, Huson SM. Psychological disturbance and sleep disorders in children with neurofibromatosis type 1. *Dev Med Child Neurol*. 2005; 47:237–42. [PubMed: 15832546]
16. Bruni O, Ottaviano S, Guidetti V, et al. The Sleep Disturbance Scale for Children (SDSC). Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. *J Sleep Res*. 1996; 5:251–61. [PubMed: 9065877]
17. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med*. 2003; 4:101–119. [PubMed: 14592341]
18. National Institutes of Health Consensus Development Conference. Neurofibromatosis: conference statement. *Arch Neurol*. 1988; 45:575–8. [PubMed: 3128965]
19. Didden R, Jeff Sigafoos J. A review of the nature and treatment of sleep disorders in individuals with developmental disabilities. *Res Dev Disabil*. 2001; 22:255–72. [PubMed: 11523951]
20. Owens JA, Spirito A, McGuinn M, Nobile C. Sleep habits and sleep disturbance in elementary school-aged children. *J Dev Behav Pediatr*. 2000; 21:27–36. [PubMed: 10706346]
21. Stein MA, Mendelsohn J, Obermeyer WH, Amromin J, Benca R. Sleep and behavior problems in school-aged children. *Pediatrics*. 2001; 107:E60. [PubMed: 11335781]
22. Ravid S, Afek I, Suraiya S, Shahar E, Pillar G. Sleep disturbances are associated with reduced school achievements in first-grade pupils. *Dev Neuropsychol*. 2009; 34:574–87. [PubMed: 20183720]
23. Beebe DW. Neurobehavioral morbidity associated with disordered breathing during sleep in children: a comprehensive review. *Sleep*. 2006; 29:1115–34. [PubMed: 17040000]

24. Kim JK, Lee JH, Lee SH, Hong SC, Cho JH. Effects of sleep-disordered breathing on physical traits, school performance, and behavior of Korean elementary school students in the upper grade levels. *Ann Otol Rhinol Laryngol*. 2012; 121:348–54. [PubMed: 22724282]
25. Potkin KT, Bunney WE Jr. Sleep Improves Memory: The Effect of Sleep on Long Term Memory in Early Adolescence. *PLoS ONE*. 2012; 7:42191. Epub.
26. Astill RG, Van der Heijden KB, Van Ijzendoorn MH, Van Someren EJ. Sleep, cognition, and behavioral problems in school-age children: a century of research meta-analyzed. *Psychol Bull*. 2012; 138:1109–38. [PubMed: 22545685]
27. Gottlieb DJ, Vezina RM, Chase C, et al. Symptoms of sleep-disordered breathing in 5-year-old children are associated with sleepiness and problem behaviors. *Pediatrics*. 2003; 112:870–7. [PubMed: 14523179]
28. Owens JA, Mindell JA. Pediatric insomnia. *Pediatr Clin North Am*. 2011; 58:555–69. [PubMed: 21600342]
29. Goldstein NA, Fatima M, Campbell TF, Rosenfeld RM. Child behavior and quality of life before and after tonsillectomy and adenoidectomy. *Arch Otolaryngol Head Neck Surg*. 2002; 128:770–5. [PubMed: 12117332]
30. Lee-Chiong TL. Parasomnias and Other Sleep-Related Movement Disorders. *Prim Care Clin Office Pract*. 2005; 32:415–434.
31. Liu X, Uchiyama M, Kim K, Okawa M, Shibui K, Kudo Y, Doi Y, Minowa M, Ogihara R. Sleep loss and daytime sleepiness in the general adult population of Japan. *Psychiatry Res*. 2000; 93(1): 1–11. [PubMed: 10699223]
32. So HK, Li AM, Au CT, Zhang J, Lau J, Fok TF, Wing YK. Night sweats in children: prevalence and associated factors. *Arch Dis Child*. 2012; 97:470–3. [PubMed: 21427123]
33. Mold JW, Woolley JH, Nagykalai Z. Associations between night sweats and other sleep disturbances: an OKPRN study. *Ann Fam Med*. 2006; 4:423–6. [PubMed: 17003142]
34. McWhinney IR. The meaning of night sweats. *Can Fam Physician*. 2005; 51:299–302. [PubMed: 15751569]
35. Goldman SE, Richdale AL, Clemons T, Malow BA. Parental sleep concerns in autism spectrum disorders: variations from childhood to adolescence. *J Autism Dev Disord*. 2012; 42:531–8. [PubMed: 21538171]
36. Wolfson AR, Carskadon MA. Sleep schedules and daytime functioning in adolescents. *Child Dev*. 1998; 69:875–87. [PubMed: 9768476]
37. Short MA, Gradisar M, Lack LC, Wright H, Carskadon MA. The discrepancy between actigraphic and sleep diary measures of sleep in adolescents. *Sleep Med*. 2012; 13:378–84. [PubMed: 22437142]
38. Williams JA, Su HS, Bernards A, Field J, Sehgal A. A circadian output in *Drosophila* mediated by neurofibromatosis-1 and Ras/MAPK. *Science*. 2001; 293:2251–6. [PubMed: 11567138]

Table 1

Sleep Disturbances in Children with Neurofibromatosis type 1 and Unaffected Siblings

Sleep Issues	Children with Neurofibromatosis type 1 (Mean $\pm$ SD)	Unaffected (Mean $\pm$ SD)	<i>P</i> *	<i>P</i> **
Total	43.49 $\pm$ 13.38	38.71 $\pm$ 9.91	<0.001	<0.001
Initiating	14.16 $\pm$ 5.65	12.37 $\pm$ 4.71	0.006	0.005
Breathing	4.49 $\pm$ 1.93	4.10 $\pm$ 1.63	0.119	0.097
Arousal	3.52 $\pm$ 0.99	3.82 $\pm$ 1.26	0.041	0.021
Transition	10.14 $\pm$ 4.13	8.78 $\pm$ 3.09	0.002	0.002
Somnolence	8.03 $\pm$ 3.38	7.42 $\pm$ 2.83	0.134	0.059
Hyperhidrosis	3.20 $\pm$ 2.01	2.35 $\pm$ 0.91	<0.001	<0.001
Average hrs of sleep	8.74 $\pm$ 1.37	9.07 $\pm$ 1.35	0.044	0.006
Time to fall sleep	31.48 $\pm$ 35.67	21.84 $\pm$ 16.48	0.009	0.011
# awakenings/night	0.85 $\pm$ 1.19	0.55 $\pm$ 0.74	0.024	0.024
# of daily naps	2.18 $\pm$ 1.42	2.17 $\pm$ 1.48	0.964	0.854

*
unadjusted p-values**
p-values after adjusting age and gender.

Table 2

Somnolence Disorders Score

Hours of sleep	Children with Neurofibromatosis type 1		Unaffected Children		<i>P</i> *
	N	Mean $\pm$ SD	N	Mean $\pm$ SD	
6 Hours	7	9.86 $\pm$ 4.53	5	12 $\pm$ 5.39	0.305
7-8Hrs	50	8.92 $\pm$ 3.72	29	7.07 $\pm$ 1.94	0.006
9-10Hrs	62	7.35 $\pm$ 2.94	42	6.69 $\pm$ 1.96	0.079
>10Hrs	10	6.50 $\pm$ 1.65	13	8.77 $\pm$ 3.77	0.152

*
p-values after adjusting age and gender

Table 3

Mean Total Sleep Score by Gender and Age

Gender/Age	Children with Neurofibromatosis type 1		Unaffected Children		P
	N	Mean ±SD	N	Mean ±SD	
Gender					
Girls	65	41.53 ± 10.85	39	37.50 ± 8.67	0.024
Boys	64	45.54 ± 15.42	50	39.67 ± 10.77	0.021
Age (years)					
2-4	26	44.96 ± 12.51	13	39.50 ± 9.50	0.138
5-9	53	42.90 ± 13.36	37	38.75 ± 9.47	0.055
10-12	24	45.00 ±14.50	17	39.19 ±12.78	0.202
13-17	26	41.76 ± 13.75	22	37.86 ± 9.07	0.263

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		<i>P</i>
	N	Mean $\pm$ SD	N	Mean $\pm$ SD	
ADHD	22	44.90 $\pm$ 13.42	104	43.54 $\pm$ 13.46	0.657
Taking Stimulant	17	45.38 $\pm$ 13.76	108	43.66 $\pm$ 13.41	0.635
IEP	19	49.11 $\pm$ 15.52	105	42.72 $\pm$ 12.84	0.107
Cognitive Impairment	61	46.09 $\pm$ 14.26	64	41.62 $\pm$ 12.41	0.075
Optic Pathway Glioma	21	48.52 $\pm$ 12.97	104	42.78 $\pm$ 13.41	0.055
Other Brain Tumor	12	41.58 $\pm$ 10.97	113	44.02 $\pm$ 13.67	0.618