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Sleep Disturbance as Part of the Neurofibromatosis Type 1 Phenotype in Adults

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Neurofibromatosis type 1 (NF1) is an autosomal dominant condition with a wide array of neurological complications, including cognitive dysfunction, tumors, malformations, neuropathy, neurovascular disease, and epilepsy. Many of these complications may impact on sleep quality and cause sleep disturbance. Previously sleep disturbance in NF1 has been specifically addressed solely in children. We performed a prospective study of sleep quality in 114 consecutive out-patients with NF1 attending our national neurofibromatosis service. The Epworth sleepiness scale (ESS) and the Pittsburgh sleep quality index (PSQI) were administered, and information was obtained from patient records on drugs potentially impacting on sleep, complications directly affecting sleep and employment status. The mean ESS was 6.8, and 21% had an abnormally high ESS of 10 or more. The mean global PSQI score was 8.4 (norm mean 2.67), with abnormally high scores in all sleep domains. Thirty-nine patients had a bed partner and 54% reported features suggestive of periodic limb movements of sleep, 43% had features suggestive of obstructive sleep apnoea, and 10.8% experienced confusion on waking. There was no evidence of phase shift. The ESS did not correlate with the PSQI, but unemployment status was associated with worse global PSQI score and multiple domain sub-scales of sleep quality in the PSQI. We conclude that sleep disturbance and poor sleep quality are significantly more frequent in the adult NF1 patient population. It is likely to be multifactorial, related to pain, anxiety, depression, cognitive issues, and organic sleep pathology. We recommend careful assessment of patients to determine underlying triggers and possible treatment strategies.

Key words: neurofibromatosis; sleep; cognition

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INTRODUCTION

Neurofibromatosis type 1 (NF1) is a common autosomal dominant condition with a birth incidence of 1 per 2,500–3,000 [Ferner, 2007]. It results from a variety of mutations in the gene encoding neurofibromin, a cytoplasmic protein that acts as a tumor suppressor and is widely expressed, especially in the nervous system [Daston et al., 1992]. The hallmark of the condition is the neurofibroma, a benign peripheral nerve sheath tumor, and cutaneous features are prominent, consisting of café au lait spots, axillary, and groin freckling. The manifestations of the disease are myriad and have a major impact on the nervous system and bone. Neurofibromin reduces cell proliferation by downregulating RAS [Xu et al., 1990].

Cognitive deficits are the commonest neurological manifestation of NF1 [Ferner et al., 1996; North et al., 1997; Hyman et al., 2005]. Typically, individuals have an IQ in the low-average range, specific learning difficulties, and behavioral problems including autistic spectrum and attention deficit hyperactivity disorder. Neurological manifestations may arise indirectly as a result of bony deformities such as sphenoid wing dysplasia causing pulsating exophthalmos, or structural abnormalities of the spine resulting in cord compression and respiratory impairment in some patients. Central nervous system tumors (gliomas) and malformations (aqueductal stenosis) may cause a variety of complications, including epilepsy [Korf et al., 1993; Ferner and Jackson, 2011], hydro-

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cephalus, and vision loss. Neurovascular abnormalities and demyelination are more common than in the general population. Neurofibromas arising from nerve roots or peripheral nerves frequently cause cord compression and neuropathy.

In our clinical practice, we have identified a high prevalence of sleep disorders in adults with NF1. Multiple factors may contribute to sleep disturbance in the adult population. These factors may be both directly or indirectly related to NF1 and its complications. Neurofibromas in and around the airway may predispose to sleep-disordered breathing [Stradling et al., 1981]. Seizures are more frequent in NF1 [Korf et al., 1993; Ferner and Jackson, 2011] and may predispose to epileptic arousals or epileptic parasomnia, and the treatment of seizures may cause either sedation or insomnia, depending on the anti-epileptic drug. Lamotrigine and levetiracetam in particular may cause insomnia. Brainstem pathology such as tumor, demyelination, or hydrocephalus, may influence sleep through lesions of nuclei controlling sleep architecture or REM atonia [Siegel, 2009]. The peripheral neuropathy associated with NF1 may predispose to restless legs syndrome and periodic limb movement disorder [Ferner et al., 2004]. Symptoms related to spinal cord compression, such as spasticity and bladder dysfunction, may cause sleep fragmentation. Pain as a result of NF1 complications may also contribute to reduced sleep quality, either directly or as a result of medication: tricyclic antidepressants used as anti-neuropathic agents can precipitate restless legs syndrome. Discomfort relating to sleeping on numerous cutaneous neurofibromas may also contribute. Furthermore, patients with NF1 have a higher incidence of psychiatric disorders, especially depression and anxiety [Mouridsen and Sorensen, 1995; Zoller and Rembeck, 1999], and indeed reduced sleep has been described in NF1, associated with mental illness [Samuelsson and Riccardi, 1989]. Both psychiatric disorders and medications used in their treatment may have a serious impact on sleep quality and disturbance [Rotenberg, 2011]. Intriguingly, null mutations of *nf1* in Drosophila result in abnormalities of circadian rhythm in locomotor activity and altered oscillations and levels of a circadian clock output protein [Williams et al., 2001]. Recognition of sleep disorders is important as these may influence features of NF1. Sleep is presumed to play an important role in memory consolidation and learning [Maquet, 2011], and sleep impairment has deleterious consequences on cognition. Impaired sleep appears to impact on pain sensitivity and analgesic effects of medications [Okifuji and Hare, 2011]. Insomnia has significant effects on quality of life [Leger et al., 2012].

There has been no previous systematic study specifically of sleep disturbance in adults with NF1, and indeed only one study in children [Johnson et al., 2005]. In this study, a postal enquiry of sleep patterns and psychological disturbance in 64 children identified a higher frequency of parasomnia as the only problem with sleep. They noted that children with sleep disturbance had a higher frequency of cognitive, emotional and behavioral problems. This is the first study to examine the frequency of sleep disturbance in NF1 adults.

METHODS

Participants were recruited from the Guy's and St. Thomas' NHS Foundation Trust general NF1 clinic and from the nationally commissioned Complex NF1 service. Trust approval was obtained (trust project no. 2225). All patients fulfilled the diagnostic criteria for NF1 [NIH Consensus Statement, 1988] and were 16 years of age or older.

Participants were asked to complete two questionnaires. The ESS [Johns, 1991] is a validated self-rated scale for the assessment of excessive daytime sleepiness. The PSQI [Buysse et al., 1989] is a validated self-rated questionnaire designed to assess sleep quality and disturbances over a 1 month period. Nineteen individual items generate seven component scores for subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. The sum of these component scores provides a global score reflective of sleep quality. Individuals with reading, language or visual difficulties were assisted by clinical nurse specialists in the completion of both questionnaires.

Patient records were examined for occupation, medications that might influence sleep quality, and medical problems that might predispose to sleep disturbance.

RESULTS

One hundred patients fully completed the PSQI and 92 participants answered the ESS; fourteen individuals were excluded due to failure to complete mandatory questions in the questionnaires. Forty-three participants were male, and 57 were female, with an age range from 16 to 69 years (mean 36.9, SD 4.7, median 36). Three families were represented, two with three patients, and one with two patients. Forty-seven patients were employed, fifteen were in school full-time and 35 were unemployed; the employment status was unknown for three patients. There were nine medical complications that potentially had a direct impact on sleep, including a low-grade brainstem glioma (n = 1) epilepsy (n = 6), non-invasive nocturnal ventilation for a large pharyngeal neurofibroma (n = 1), and for severe scoliosis causing respiratory compromise (n = 1).

The mean ESS (n = 92) was 6.8 (95% CI 5.8–7.9; two-tailed $P = 0.07$ compared to normative mean 5.9). Nineteen patients reported an ESS of >9. Analysis of PSQI data (n = 100) demonstrated significant differences between the patient cohort and normative values for the global PSQI score and all sleep domain component scores ($P < 0.001$ in all tests; Table I). Mean actual sleep duration was 6.44 hr, mean bed-time was 22:49, and mean wake-up time was 7.28 am. Commonest symptoms complained about were difficulty getting to sleep within 30 min (n = 85) and waking up in the middle of the night or early morning (n = 90). These problems were reported on three or more nights per week by 43 and 47 patients, respectively. In contrast, difficulty breathing, coughing or snoring loudly were only reported by 18 and 25 patients, respectively. Pain was reported by 49 patients, with 25 reporting difficulty sleeping due to pain on three or more nights per week (Table II). Nocturnal itching was not reported by any patient.

In the non-mandatory section of the PSQI questionnaire, 59 patients reported no bed partner or room mate, two had a partner or house mate in a different room, one reported a bed partner in the same room but different bed, 36 reported sharing a bed, and two did not answer. Thirty-seven individuals answered questions 10a–e, regarding symptoms reported by their bed-partner/room-mate.

TABLE I. ESS and PSQI Scores for Patient Cohort and Normative Means, Derived From Johns [1991] and Buysse et al. [1989]

Measure	Patient mean (SD)	Normative mean	*t*-Test 2-tailed *P*-value
ESS	6.83 (4.97)	5.9	0.07
PSQI global	8.44 (4.59)	2.67	<0.001
PSQI duration	1.07 (1.14)	0.29	<0.001
PSQI disturbance	1.40 (0.59)	1	<0.001
PSQI latency	1.83 (0.99)	0.56	<0.001
PSQI daytime dysfunction	1.11 (0.86)	0.35	<0.001
PSQI sleep efficiency	1.15 (1.27)	0.1	<0.001
PSQI sleep quality	1.46 (0.86)	0.35	<0.001
PSQI sleep medication	0.42 (0.95)	0.04	<0.001

Sixteen had snored in the last month, twelve at least once or twice a week. Seven had been noted to stop breathing in their sleep, although only one was noted not to snore. Twenty patients had twitching or jerking of their legs while asleep, 10 reporting this three times per week or more. Four patients had been confused on waking in the previous month, two more than once or twice weekly.

There was no significant correlation between PSQI score and ESS ($r = 0.18$, $P = 0.085$). There was no significant correlation between the patients taking medication that may influence sleep and either the PSQI score ($r = -0.19$, $P = 0.065$) or the ESS ($r = 0.03$, $P = 0.790$).

ANOVA demonstrated that unemployment status was significantly associated with a worse global PSQI score ($P = 0.001$). Unemployment was also associated with multiple component domains of worse sleep quality in the PSQI. No significant relationship was found between employment status and ESS.

DISCUSSION

Our prospective study is the first to identify a high frequency of sleep disturbance and excessive daytime sleepiness in adults with NF1, utilizing the validated ESS and the PSQI. The NF1 patient cohort comprised 43 males and 57 females with a wide age range and variable disease severity. Excessive daytime sleepiness was reported in 20.7% on the ESS, and 69% exhibited a global PSQI score of >5, implying that they are "poor sleepers" [Buysse et al., 1989]. All mean component scores and the global score for the PSQI were significantly greater than in a normal population. The commonest self-reported sleep difficulties were difficulty getting to sleep within 30 min, and waking in the middle of the night or early morning. Features suggestive of periodic limb movements were reported in 54% of individuals with a bed partner or room mate, 43% described features suggestive of sleep-disordered breathing, and 10.8% reported confusion on waking, suggestive of nocturnal seizures or a parasomnia. The corroborative history in one individual reported witnessed pauses in breathing in the absence of snoring, perhaps indicative of central sleep apnea. Mean bed-time and wake-up time did not suggest phase shift indicative of circadian rhythm abnormalities. There was no evidence suggesting that sleep disturbance or poor sleep quality was influenced by medications.

Of note, there was no association between ESS and PSQI scores. The PSQI, but not the ESS, was associated with employment status;

TABLE II. Responses to Questions 5a to 5i of the PSQI, Describing How Often the Subject Has Difficulty Sleeping Due to the Symptom in the Last Month

Symptom causing trouble sleeping	Not during past month	Less than once per week	Once or twice per week	Three or more times per week
Cannot sleep within 30 min	15	24	18	43
Wake in night or early morning	10	19	24	47
Get up to use bathroom	28	19	24	29
Cannot breathe comfortably	82	6	5	7
Cough or snore loudly	75	7	5	13
Feel too cold	67	17	7	9
Feel too hot	44	15	23	18
Bad dreams	59	23	15	3
Pain	51	14	10	25

a worse PSQI was seen in the unemployed group, sleep quality as measured by the PSQI was best in those in employment. Excessive daytime sleepiness, as measured by the ESS, is often used as a discriminator to differentiate patients with sleep disorders, such as sleep apnea and periodic limb movement disorder, from those with psycho-physiological insomnia or insomnia related to psychological state. These results imply that there may be two groups in the cohort: those with excessive daytime sleepiness related to an organic sleep pathology, and a second group of "poor sleepers." This second group is likely to represent individuals with multifactorial sleep disturbance, perhaps related to factors such as cognitive and emotional problems, pain, and anxiety. It is hypothesized that employment status is a marker of cognitive function or psychological status, albeit an imprecise one. This would be in keeping with previous findings in the pediatric population [Johnson et al., 2005], demonstrating that sleep disturbance is commoner in children with cognitive issues, and a single study in adults with NF1, demonstrating an association between reduced sleep and psychiatric illness [Samuelsson and Riccardi, 1989]. Further work is required to ascertain the validity of this hypothesis. Sleep quality needs to be compared to validated measures of psychological state, especially anxiety and depression, more direct measures of cognitive function and behavioral function [North et al., 1997], careful characterization of phenotypic issues such as neurofibroma load, measures of quality of life with disease-specific questionnaires, and objective measures of organic sleep pathology, with polysomnographic studies.

In conclusion, we have identified a high frequency of sleep disturbance, impaired sleep quality and excessive daytime sleepiness in adults with NF1. Sleep disturbance is a potent cause of impaired quality of life and we recommend careful assessment of sleep in people with NF1 to determine the underlying medical and psychological causes.

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