

SLEEP PATTERNS IN NEUROFIBROMATOSIS TYPE 1: A QUESTIONNAIRE  
BASED APPROACH

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## **ABSTRACT**

**Background:** Neurofibromatosis type 1 (NF1) is a common genetic disorder that manifests in early childhood. Although not a classical manifestation, NF1 has been associated with sleep problems in children, which could have a major impact in their day-to-day life and compromise their future. We set out to assess whether there is a higher prevalence of sleep disturbances in children with NF1, as compared to children without the disease.

**Methods:** We applied the Portuguese version of the Children's Sleep Habits Questionnaire (CSHQ) in order to evaluate the sleep quality of children aged 2-10 years old. The CSHQ was distributed in primary schools and preschools throughout the country and also via e-mail to the members of the Portuguese Neurofibromatosis Association. We divided the participants into the NF1 group and the control group, based on whether they had been diagnosed with NF1 or not, and compared the results with standard statistical analysis.

**Results:** We observed no difference in the CSHQ Total Score between groups ( $p=0.176$ ). However, we did find higher scores in the NF1 group in the subscales Sleep Duration ( $p=0.006$ ), Night Wakings ( $p=0.041$ ) and Sleep-Disordered Breathing ( $p=0.009$ ), compared to the controls. We also found Sleep Duration (AUROC=0.690;  $p=0.018$ ) and Sleep-Disordered Breathing (AUROC=0.677;  $p=0.028$ ) subscales to have predictive value for the NF1 group, more so when combined.

**Discussion:** We observed a higher prevalence of specific sleep disturbances in children with NF1, although not a global sleep impairment. We hypothesize that these findings are consistent with the notion that sleep disturbances are associated with a dysfunctional default mode network (DMN) in individuals with NF1.

**Keywords:** Children's Sleep Habits Questionnaire; Cross-Sectional Studies; Default Mode Network; Neurofibromatosis 1; Sleep Disorders.

## RESUMO

**Introdução:** A neurofibromatose do tipo 1 (NF1) é uma doença genética relativamente comum que se manifesta na infância precoce. Embora não seja um sintoma clássico, a NF1 foi associada a problemas de sono em crianças, que podem ter um impacto negativo no seu dia-a-dia e prejudicar o seu futuro. No presente estudo, nós propusemo-nos a averiguar se haverá uma maior prevalência de distúrbios do sono em crianças com NF1, relativamente a crianças sem a doença.

**Métodos:** Aplicámos a versão portuguesa do *Children's Sleep Habits Questionnaire* (CSHQ) para avaliar a qualidade do sono de crianças com idades compreendidas entre 2-10 anos. O CSHQ foi distribuído em escolas primárias e jardins-escola pelo país e também via correio electrónico para os membros da Associação Portuguesa de Neurofibromatose. Dividimos os participantes em dois grupos, o grupo NF1 e o grupo de controlo, consoante tinham ou não sido diagnosticados com NF1, e comparámos estatisticamente os resultados.

**Resultados:** Não encontramos diferenças na Pontuação Total do CSHQ entre grupos ( $p=0.176$ ). No entanto, observámos pontuações mais elevadas no grupo NF1 nas subescalas Duração do Sono ( $p=0.006$ ), Despertares Nocturnos ( $p=0.041$ ) e Perturbação Respiratória do Sono ( $p=0.009$ ), relativamente aos controlos. Também verificámos que as subescalas Duração do Sono (AUROC=0.690;  $p=0.018$ ) e Perturbação Respiratória do Sono (AUROC=0.677;  $p=0.028$ ) têm capacidade preditiva para o grupo NF1, com maior efeito quando combinadas.

**Discussão:** Observámos uma maior prevalência de perturbações do sono específicas em crianças com NF1, mas não uma perturbação generalizada do sono. Nós especulamos que estes achados são consistentes com a noção de que as perturbações do sono estão associadas à disfunção da *default mode network* (DMN) em indivíduos com NF1.

**Palavras-chave:** Children's Sleep Habits Questionnaire; Estudo Transversal; Default Mode Network; Neurofibromatose 1; Distúrbios do Sono.

## **ACRONYMS**

ADHD	Attention deficit/hyperactivity disorder
AUROC	Area under ROC curve
CSHQ	Children's Sleep Habits Questionnaire
DMN	Default-mode network
fMRI	Functional Magnetic Resonance Imaging
NF1	Neurofibromatosis type 1

## BACKGROUND

Neurofibromatosis type 1 (NF1) is a common genetic disorder that affects 1 in 3000 to 3500 people.[1] It is caused by a mutation in the *NF1* gene, located on chromosome 17, that can be inherited in an autosomal dominant pattern or emerge as a *de novo* mutation.[2] NF1 has a penetrance of 100% by the age of twenty years,[1] but its expression is highly variable.[3] More than 1485 mutations have been identified but no clear link between genotype and phenotype has been established, save rare exceptions. The NF1 gene encodes the protein neurofibromin, which has an important role in the regulation of cell growth and proliferation, acting as a tumor suppressor through the inhibition of RAS signal transduction pathway. The impaired expression of neurofibromin in NF1 results in unrestricted cell proliferation and is, therefore, associated with an increased risk of tumor formation.[2,3]

NF1 frequently manifests in early childhood and its diagnosis is essentially clinical.[1] Common manifestations include café-au-lait spots, inguinal and/or axillary freckling, iris hamartomas (Lisch nodules), neurofibromas, optic pathway gliomas, skeletal and cardiovascular deformities and neurocognitive deficits. The latter are extremely frequent in individuals with NF1 and they represent a major impediment in day-to-day life.[1,4] Several studies [5,6] have shown a predominance of specific difficulties in different areas of cognition rather than a global intellectual deficit in individuals with NF1, namely language, memory and attention problems, visuospatial perception impairment, executive functioning deficits, among others. A higher prevalence of attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorders has also been described. In affected children, cognitive deficits have a negative impact on school performance, social development and emotional adjustment, potentially jeopardizing their academic future and overall quality of life.[5,6]

Sleep disturbances are not classically considered manifestations of NF1. Johnson et al.[7] found a higher prevalence of sleep problems in children with NF1, however, no recent

studies have been dedicated to clarifying this relationship. Sleep disturbances can manifest in children as excessive daytime sleepiness, poor concentration, decreased attention, depressed mood, behavioral problems, learning difficulties and poor academic performance.[8] As several of these symptoms can also appear in children with NF1, concomitant sleep disturbances in these individuals may exacerbate preexisting cognitive deficits and, if unrecognized or untreated, could worsen the child's prognosis. It is, therefore, of vital importance to ascertain whether the occurrence of sleep problems is directly related to NF1 and, if so, how it may affect the patients' everyday life.

The purpose of this study is to assess whether there is a higher prevalence of sleep disturbances in children with NF1, when compared to children without the disease.

## **METHODS**

### **Enrollment of Participants**

Children between the ages of 2 and 10 years old were randomly selected from two primary schools and two preschools in different regions of Portugal (Portalegre, Braga and Leiria). One-hundred and seventeen questionnaires were delivered to the parents of these children through their class teachers, from the 2-year-old class in preschools to the 4<sup>th</sup> grade class in primary schools, with the authorization of the respective school directors. Ninety questionnaires (76.9%) were returned, from which 16 were incomplete and 5 matched exclusion criteria. The 69 remaining questionnaires (59.0%) were included in the study. The questionnaires were distributed and received from May 15<sup>th</sup> 2014 until July 30<sup>th</sup> 2014.

An online version of the questionnaire was disclosed through the mailing list of the Portuguese Neurofibromatosis Association (*Associação Portuguesa de Neurofibromatose*) in order to recruit subjects for the NF1 study group. There were 20 replies, from which two did not fit the age range and two matched exclusion criteria. The 16 remaining questionnaires

were included in the study. The online questionnaire was made available on July 8<sup>th</sup> 2014 and replies were received until August 30<sup>th</sup> 2014.

### **Inclusion and Exclusion Criteria**

The inclusion criteria considered were the child's age, from 2 through 10 years old, and the consent from the parents or legal guardians. The selection of the NF1 study group was based on the child's Neurofibromatosis type 1 diagnosis reported by the parents. This study was within the scope of grant PTDC/SAU-ORG/118380/2010 and its ethical approval.

The exclusion criteria included medications or conditions that might impact the quality or pattern of sleep, such as ADHD, autism spectrum disorders, complex neurological disorders, psychiatric disorders and unstable chronic disorders (e.g., epilepsy, asthma). All seven cases that matched exclusion criteria involved the regular use of potentially sleep-altering medication (e.g., Singulair®, Xyzal®, Rubifen®, Zyrtec®, Risperdal®, Tegretol®).

### **Participants' characteristics and sleep environment**

Information concerning the participants' family sociodemographic characteristics and regarding the children's sleep environment and routine was collected through a series of questions included in the questionnaire delivered to the parents (Attachment A).

### **Children's Sleep Habits Questionnaire**

In order to evaluate the sleep quality of children with and without Neurofibromatosis type 1, the Portuguese version of Owens' "Children's Sleep Habits Questionnaire" (CSHQ)[9,10] was applied (Attachment A). The CSHQ is a retrospective parent-report of the child's sleep habits in a typical recent week. It is composed of 33 items, each scoring from 1 to 3, which can be grouped into eight basic sleep domains: Bedtime Resistance, Sleep Onset Delay, Sleep Duration, Sleep Anxiety, Night Wakings, Parasomnias, Sleep-Disordered Breathing and Daytime Sleepiness.



The Total Score (i.e., the combined score of the 33 items) translates the global quality of sleep. Higher scores are indicative of a more disturbed sleep, and vice-versa. In the original study,[9] a cut-off score of 41 was determined to have diagnostic value in identifying children with sleep disorders. The Portuguese validation study [10] concluded that the Portuguese version of the CSHQ showed acceptable psychometric properties for the screening of sleep problems in children aged 2 through 10 years old.

### **Statistical Analysis**

The data analysis was performed using SPSS Statistics 17.0 program. The significance level was established at  $p < 0.05$ . Statistical descriptions comprised the mean, standard deviation and median for quantitative variables, and frequencies and percentages for nominal variables. T-Student and Mann-Whitney U tests were used to compare means of continuous variables such as age and CSHQ scores. Chi-square test, Fisher's Exact Test and Montecarlo correction were used to compare frequencies of categorical sociodemographic and sleep related factors. ROC curve analysis was used to assess the predictive value of CSHQ Total Score and subscales for the NF1 group. Associations between CSHQ subscales were determined using Spearman's correlation analysis. Logistic regression was applied in order to calculate odds ratios.

## **RESULTS**

### **Participants' sociodemographic characteristics, sleep environment and sleep routine**

As depicted in Table 1, 86 children participated in the present study. They were divided into the control group (n=70, 35 girls and 35 boys) and the NF1 group (n=16, 7 girls and 9 boys). The age and gender of participants did not differ between groups, nor did the parent's age, level of education, marital status and employment situation.

Table 1 - Sociodemographic characterization

Variables	Control group n=70	NF1 group n=16	P value
Gender			0.652‡
Male	35 (50.0)	9 (56.3)	
Female	35 (50.0)	7 (43.8)	
Age			
Participant	5.83 ± 2.467	4.56 ± 2.220	0.064†
Mother	36.90 ± 5.754	34.56 ± 4.761	0.123†
Father <sup>1</sup>	37.96 ± 5.371	35.56 ± 6.055	0.121*
Parents' marital status			1.000§
Married / civil union	61 (87.1)	14 (87.5)	
Divorced	5 (7.1)	1 (6.3)	
Single mother / father	4 (5.7)	1 (6.3)	
Mother's work status			0.450§
Unemployed	10 (14.3)	3 (18.8)	
Part-time work	7 (10.0)	0 (0.0)	
Full-time work	53 (75.7)	13 (81.3)	
Father's work status			1.000§
Unknown	2 (2.9)	0 (0.0)	
Unemployed	5 (7.1)	1 (6.3)	
Part-time work	1 (1.4)	0 (0.0)	
Full-time work	62 (88.6)	15 (93.8)	
Mother's education			0.856†
Basic education	12 (17.1)	3 (18.8)	
Secondary education	26 (37.1)	5 (31.3)	
Higher education	32 (45.7)	8 (50.0)	
Father's education <sup>1</sup>			0.381†
Basic education	20 (29.4)	3 (18.8)	
Secondary education	28 (41.2)	7 (43.8)	
Higher education	20 (29.4)	6 (37.5)	

The data are presented as number (%) or mean ± standard-deviation.

<sup>1</sup>In "Age - Father" and "Father's education", sample size in the control group is n=68

\*T-Student Test

† Mann-Whitney U Test

‡ Chi-Square Test

§ Chi-Square Test with Monte-Carlo Correction

The children's sleep environment was similar in both groups, with no differences regarding the type of residence, siblings, room sharing and co-sleeping. However, there was a difference in the population density of the participants' area of residence, as all children in the NF1 group lived in urban settings (Table 2).

Table 2 - Sleep environment

Variables	Control group n=70	NF1 group n=16	P value
Residence			0.313 <sup>§</sup>
Apartment	46 (65.7)	13 (81.3)	
Row house	7 (10.0)	2 (12.5)	
Unattached house	17 (24.3)	1 (6.3)	
Population density			< 0.001 <sup>‡</sup>
Rural ( $\leq 100/\text{Km}^2$ )	40 (57.1)	0 (0.0)	
Urban ( $> 100/\text{Km}^2$ )	30 (42.9)	16 (100.0)	
Child has siblings			0.236 <sup>‡</sup>
No	28 (40.0)	9 (56.3)	
Yes	42 (60.0)	7 (43.8)	
Child has single room			0.309**
No	4 (5.7)	2 (12.5)	
Yes	66 (94.3)	15 (87.5)	
Falls asleep on parent's bed			0.505**
No	53 (75.7)	14 (87.5)	
Yes	17 (24.3)	2 (12.5)	

The data are presented as number (%) or mean  $\pm$  standard-deviation.

\*\*Fisher's Exact Test

‡ Chi-Square Test

§ Chi-Square Test with Monte-Carlo Correction

Children with NF1 were reported to wake up earlier, both in week days and in the weekend, and take naps more frequently than children in the control group, however, reported total sleep time was similar. There were no statistical differences concerning other sleep routines between groups (Table 3).

Table 3 - Sleep routine

Variables	Control group n = 70	NF1 group n = 16	P value
Child has bedtime routine			0.116**
No	4 (5.7)	3 (18.8)	
Yes	66 (94.3)	13 (81.3)	
Child takes naps			<b>0.014**</b>
No	54 (77.1)	7 (43.8)	
Yes	16 (22.9)	9 (56.3)	
Who puts the child to bed			0.249§
Father	3 (4.3)	2 (12.5)	
Mother	30 (42.9)	3 (18.8)	
Both parents	23 (32.9)	8 (50.0)	
Child goes by him/herself	11 (15.7)	3 (18.8)	
Other	3 (4.3)	0 (0.0)	
Parents are present when child falls asleep			0.652‡
No	35 (50.0)	7 (43.8)	
Yes	35 (50.0)	9 (56.3)	
Bedtime			
Week	21:40h ± 34m	21:46h ± 39m	0.476†
Weekend	22:24h ± 41m	22:19h ± 44m	0.538†
Wake time			
Week	7:50h ± 28m	7:23h ± 59m	<b>0.001</b> †
Weekend	9:00h ± 58m	8:11h ± 82m	<b>0.010</b> †
Total daily sleep time (including naps)	10.33h ± 1.156	10.19h ± 1.548	0.565†

The data are presented as number (%) or mean ± standard-deviation.

\*\*Fisher's Exact Test

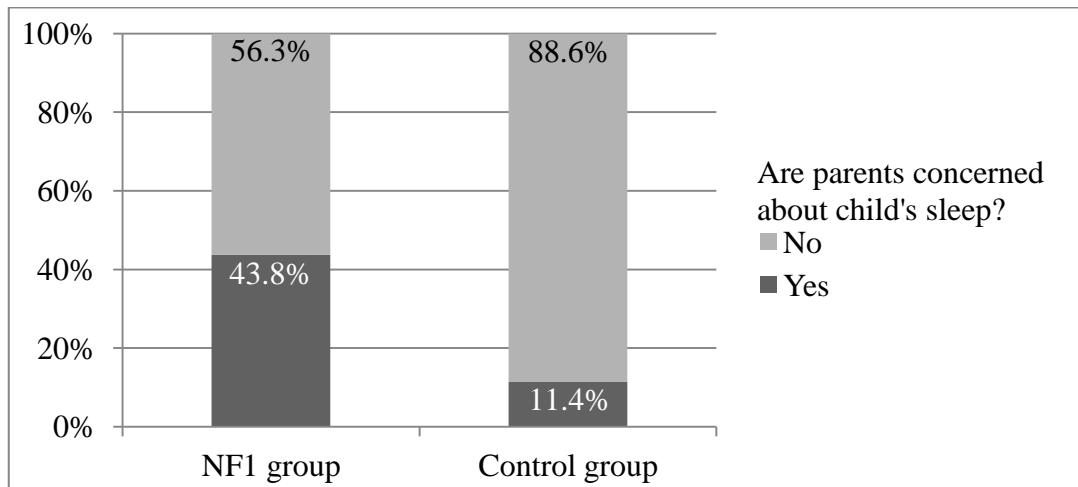
† Mann-Whitney U Test

‡ Chi-Square Test

§ Chi-Square Test with Monte-Carlo Correction

The parents were asked whether they were concerned about their child's quality of sleep (Figure 1) and the answers differed between the control group and the NF1 group, revealing a greater concern about sleep problems from parents of children with NF1 ( $p = 0.006$ ).

Figure 1 - Comparison of parents' concern with child's sleep between NF1 and control groups



### The Children's Sleep Habits Questionnaire

We analyzed the results of the CSHQ, comparing the scores of the NF1 group with the ones reported by the control group.

The Total Score did not differ statistically between the NF1 group and the control group ( $p=0,176$ ), but we observed a tendency for higher scores in the NF1 group (Table 4).

When evaluating the CSHQ subscales, we found that Sleep Duration ( $p=0,006$ ), Night Wakings ( $p=0,041$ ) and Sleep-Disordered Breathing ( $p=0,009$ ) scores were significantly higher in the NF1 group than in the control group. No differences were observed in the subscales Bedtime Resistance ( $p=0.330$ ), Sleep Onset Delay ( $p=0.680$ ), Sleep Anxiety ( $p=0.742$ ), Parasomnias ( $p=0.125$ ) or Daytime Sleepiness ( $p=0.057$ ) between groups. Analyzing the items that compose Sleep Duration, Night Wakings and Sleep-Disordered Breathing, we found that, in the NF1 group, children were more frequently reported to sleep scantily (item 9,  $p<0.001$ ), to have an irregular sleep duration (item 11,  $p=0.034$ ), to wake up once or more during the night (item 24,  $p=0.037$ , and item 25,  $p=0.001$ ), to snore loudly (item 18,  $p=0.007$ ) and to experience sleep apneas (item 19,  $p=0.039$ ), when compared to controls.

Table 4 - Children's Sleep Habits Questionnaire

CSHQ	Control group n = 70	NF1 group n = 16	P value
Total Score	46.5 ± 6.449	49.0 ± 7.303	0.176*
Subscales			
Bedtime Resistance	8.81 ± 3.013 [8.0]	9.31 ± 2.600 [9.0]	0.330†
Sleep Onset Delay	1.76 ± 0.859 [1.0]	1.63 ± 0.719 [1.5]	0.680†
Sleep Duration	3.49 ± 0.913 [3.0]	4.56 ± 1.750 [4.0]	<b>0.006</b> †
Sleep Anxiety	6.04 ± 1.899 [6.0]	5.88 ± 1.821 [5.5]	0.742†
Night Wakings	3.83 ± 1.154 [3.0]	4.56 ± 1.504 [4.5]	<b>0.041</b> †
Parasomnias	9.01 ± 1.655 [9.0]	9.88 ± 2.029 [10.0]	0.125†
Sleep-Disordered Breathing	3.60 ± 1.345 [3.0]	4.44 ± 1.825 [4.0]	<b>0.009</b> †
Daytime Sleepiness	13.16 ± 2.981 [13.0]	11.56 ± 1.931 [12.0]	0.057†

The data are presented as mean ± standard-deviation or mean ± standard-deviation [median]

\* T-Student Test

† Mann-Whitney U Test

The ROC curve analysis showed us that the subscales Sleep Duration (AUROC=0.690; p=0.018) and Sleep-Disordered Breathing (AUROC=0.677; p=0.028) had predictive value for the NF1 group (Table 5), thus strengthening the association between these altered sleep domains and NF1. We found no correlation between these two subscales (p=0.279), using Spearman's correlation analysis. Hence, we set out to analyze the separate and combined capability of these subscales in predicting the NF1 group, using logistic regression and ROC curve analysis. The odds ratios are described in Table 6. We noticed that the combined score of Sleep Duration and Sleep-Disordered Breathing (Table 5) had a greater predictive value for the NF1 group (AUROC=0.783; p<0.001) than that of the isolated subscales.

Table 5 - Predictive value of CSHQ Total Score and subscales for NF1 group

CSHQ	NF1 group	
	AUROC*	P value
Total Score	0.628	0.111
Bedtime Resistance	0.577	0.340
Sleep Onset Delay	0.470	0.706
Sleep Duration	0.690	<b>0.018</b>
Sleep Anxiety	0.474	0.748
Night Wakings	0.652	0.059
Parasomnias	0.621	0.131
Sleep-Disordered Breathing	0.677	<b>0.028</b>
Daytime Sleepiness	0.348	0.058
Sleep Duration + Sleep-Disordered Breathing	0.783	<b>&lt;0.001</b>

\* AUROC - area under ROC curve

Table 6 - Association between Sleep Duration and Sleep-Disordered Breathing and the diagnosis of NF1

CSHQ	Odds Ratio	P value
Sleep Duration	1.860	<b>0.004</b>
Sleep-Disordered Breathing	1.353	0.075

## DISCUSSION

We set out to explore the occurrence of sleep problems in children with NF1, comparing with controls. As we expected, we found a higher prevalence of sleep disturbances in specific sleep domains in children with NF1, although not a global sleep impairment. The affected sleep domains were Sleep Duration, Sleep-Disordered Breathing and, to a lesser extent, Night Wakings. The disturbance of specific sleep domains fits the NF1 clinical profile, similarly to the neurocognitive manifestations which usually comprise specific deficits rather than a global impairment.

We hypothesize that both these conditions, NF1 and sleep disturbances, may be connected through an underlying mechanism - a dysfunction of the default mode network (DMN). The DMN is a neuronal network which is primarily active when the brain is at rest (task-negative state), promoting self-referential thought (i.e., internal mentation, daydreaming), and deactivates during cognitive demanding tasks.[11,12] DMN dysfunction, whether through excessive activation or inadequate deactivation, may result in impaired cognitive performance and has been shown to be involved in several neuropsychological disorders.[12]

Recent studies have proposed the involvement of the DMN both in NF1 and in insomnia. Violante *et al.*[13] discovered a dysfunction in the DMN in patients with NF1, theorizing its involvement in the pathogenesis of the cognitive deficits frequently found in these individuals. On the other hand, Marques *et al.*[14] suggested a contributing role of DMN dysfunction in the onset and maintenance of insomnia.

Thus, we believe DMN dysfunction to be a primary physiopathological process in NF1, possibly underlying an increased prevalence of specific sleep disorders in affected children.

### **Limitations**

A major limitation of the present study is the sample size of the NF1 group. A target enrollment of 26 children for the NF1 group and 26 for the control group was projected, derived from a sample-size calculation using  $\alpha = 0.05$ , power of 0.80 and a large effect size. However, only 16 participants were gathered in the NF1 group, lowering the power of the study to only about 0.43.

Another limitation is the reliance on the parents' report alone to evaluate sleep quality, while other methods, such as polysomnography, would allow for a more objective and accurate assessment of sleep.



Also, we cannot exclude environmental factors, such as the population density of the participants' area of residence, as a source of bias.

### **Future directions**

We believe this subject warrants a deeper investigation, through a more detailed analysis of sleep using polysomnography in children with NF1 and a proper neuropsychological evaluation in order to characterize cognitive deficits, assess their severity and impact in the children's lives, and expose their association with disturbed sleep.

We also believe it would be valuable to further explore the role of DMN dysfunction in the physiopathology of NF1 and its association with cognitive deficits and sleep disturbances, using functional neuroimaging techniques such as fMRI.

### **Conflict of Interest**

The authors declare no conflict of interest.

### **ACKNOWLEDGMENTS**

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## REFERENCES

1. Couto C, Monteiro T, Araújo L, Temudo T. Neurofibromatose tipo 1: diagnóstico e seguimento em idade pediátrica. *Acta Pediátrica Portuguesa*. 2012;43(2):75-83.
2. Abramowicz A, Gos M. Neurofibromin in neurofibromatosis type 1 - mutations in *NFI* gene as a cause of disease. *Developmental period medicine*. 2014;18(3):297-306.
3. Pasmant E, Vidaud M, Vidaud D, Wolkenstein P. Neurofibromatosis type 1: from genotype to phenotype. *Journal of medical genetics*. 2012;49(8):483-9.
4. Hirbe AC, Gutmann DH. Neurofibromatosis type 1: a multidisciplinary approach to care. *The Lancet Neurology*. 2014;13(8):834-43.
5. Diggs-Andrews KA, Gutmann DH. Modeling cognitive dysfunction in neurofibromatosis-1. *Trends in neurosciences*. 2013;36(4):237-47.
6. Templer AK, Titus JB, Gutmann DH. A neuropsychological perspective on attention problems in neurofibromatosis type 1. *Journal of attention disorders*. 2013;17(6):489-96.
7. Johnson H, Wiggs L, Stores G, Huson SM. Psychological disturbance and sleep disorders in children with neurofibromatosis type 1. *Developmental medicine and child neurology*. 2005;47(4):237-42.
8. Carter KA, Hathaway NE, Lettieri CF. Common sleep disorders in children. *American family physician*. 2014;89(5):368-77.
9. Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): psychometric properties of a survey instrument for school-aged children. *Sleep*. 2000;23(8):1043-51.
10. Silva FG, Silva CR, Braga LB, Neto AS. Portuguese Children's Sleep Habits Questionnaire - validation and cross-cultural comparison. *Jornal de pediatria*. 2014;90(1):78-84.

11. Anticevic A, Cole MW, Murray JD, Corlett PR, Wang XJ, Krystal JH. The role of default network deactivation in cognition and disease. *Trends in cognitive sciences.* 2012;16(12):584-92.
12. Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJ. Default-mode brain dysfunction in mental disorders: a systematic review. *Neuroscience and biobehavioral reviews.* 2009;33(3):279-96.
13. Violante IR, Ribeiro MJ, Cunha G, Bernardino I, Duarte JV, Ramos F, Saraiva J, Silva E, Castelo-Branco M. Abnormal brain activation in neurofibromatosis type 1: a link between visual processing and the default mode network. *PloS one.* 2012;7(6):e38785.
14. Marques DR, Gomes AA, Clemente V, Santos JM, Castelo-Branco M. Default-mode network activity and its role in comprehension and management of psychophysiological insomnia: A new perspective. *New Ideas in Psychology.* 2015;36:30-7.

# **ATTACHMENTS**



## QUESTIONÁRIO SOBRE HÁBITOS DE SONO EM CRIANÇAS

O presente questionário enquadra-se num estudo realizado no âmbito de uma dissertação de Mestrado Integrado em Medicina com a colaboração do Instituto de Imagem Biomédica e Ciências da Vida (IBILI). Com este estudo pretende-se investigar as diferenças entre os hábitos de sono de crianças com Neurofibromatose do Tipo I e os hábitos de sono de crianças saudáveis. O questionário diz respeito a crianças com idades compreendidas entre os 2 e os 10 anos e deverá ser preenchido por um ou ambos os pais ou pela pessoa responsável pela criança.

É importante que saiba que **a decisão em participar neste estudo é inteiramente voluntária** e que a sua decisão, seja ela qual for, não poderá prejudicá-lo(a) de forma alguma. O **anonimato dos participantes será sempre preservado** e os dados serão informatizados e tratados sob a responsabilidade do IBILI, podendo o voluntário aceder à informação que lhe diz respeito por solicitação junto do investigador principal (Professor Doutor Miguel Castelo-Branco) e requerer a sua atualização, correção ou eliminação. As informações fornecidas no questionário serão, assim, utilizadas somente para análise estatística, sendo garantida a confidencialidade das respostas. A identidade dos participantes não será revelada em quaisquer relatórios ou publicações resultantes deste estudo.

Este estudo foi aprovado pela Comissão de Ética da Faculdade de Medicina da Universidade de Coimbra (FMUC) de modo a garantir a protecção dos direitos de todos os doentes ou outros participantes incluídos e garantir prova pública dessa protecção.

Deste modo, é convidado(a) a participar voluntariamente neste estudo, através do preenchimento do questionário que se segue, que não deverá exceder 10 minutos.

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Os investigadores responsáveis pelo estudo estarão ao seu dispor para lhe responder a qualquer dúvida ou esclarecimento que necessite:

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## DECLARAÇÃO DE CONSENTIMENTO INFORMADO

Eu, \_\_\_\_\_ ,  
mãe/pai de \_\_\_\_\_ , compreendo a informação que  
me foi fornecida na folha informativa, esclareci as minhas dúvidas e concordo que o meu /minha  
filho(a) participe no estudo acima referido.

Antes do início da avaliação foi-me explicado o protocolo do estudo. O anonimato será  
preservado e a minha participação é voluntária.

Lisboa, \_\_\_\_ de \_\_\_\_\_ de \_\_\_\_\_

Ass: \_\_\_\_\_

Encarregado de educação do participante

Ass: \_\_\_\_\_

O investigador

Código

1

Código

Este questionário deve ser preenchido por um dos pais ou por outra pessoa que cuide da criança e conheça bem os seus hábitos de sono. A criança deve ter entre 2 e 10 anos de idade, inclusive. Por favor, responda a todas as questões. Inquéritos incompletos não poderão ser utilizados no estudo.

Nesta primeira parte do inquérito, ser-lhe-ão pedidos dados acerca da criança e da sua família. Nas questões de escolha múltipla, assinale com uma cruz **apenas 1 opção**.

**As questões que se seguem dizem respeito aos pais:**

Estado civil dos pais

- Casados / em união de facto
- Divorciados
- Mãe solteira / pai solteiro

Idade da mãe: \_\_\_\_\_

Idade do pai: \_\_\_\_\_

Situação profissional da mãe

- Desempregada
- Trabalho em part-time
- Trabalho a tempo inteiro

Situação profissional do pai

- Desempregado
- Trabalho em part-time
- Trabalho a tempo inteiro

Nível de escolaridade da mãe

- Ensino básico (1º ao 9º ano)
- Ensino secundário (10º ao 12º ano)
- Licenciatura, Mestrado ou Doutoramento

Nível de escolaridade o pai

- Ensino básico (1º ao 9º ano)
- Ensino secundário (10º ao 12º ano)
- Licenciatura, Mestrado ou Doutoramento

**As questões que se seguem dizem respeito à criança:**

Sexo da criança

Masculino

Feminino

Idade da criança: \_\_\_\_\_

Data de nascimento: \_\_\_\_/\_\_\_\_/\_\_\_\_

Local de residência (concelho/distrito): \_\_\_\_\_

A criança reside em:

Apartamento

Casa geminada

Vivenda

Tem irmãos?

Sim

Não

Tem quarto próprio?

Sim

Não

A criança adormece na cama dos pais?

Sim

Não

A criança tem uma rotina na hora de ir para a cama?

Sim

Não



A criança tem o hábito de fazer sestas durante o dia?

Sim

Não

Quem deita a criança à noite?

Quase sempre o pai

Quase sempre a mãe

Umhas vezes o pai e noutras a mãe

A criança vai deitar-se sozinha

Outro - Quem? \_\_\_\_\_

Algum dos pais (ou ambos) está presente quando a criança adormece?

Frequentemente

Raramente

Qual é a hora a que a criança habitualmente se deita?

- Durante a semana: \_\_\_\_\_

- Durante o fim-de-semana: \_\_\_\_\_

Qual é a hora a que a criança habitualmente acorda?

- Durante a semana: \_\_\_\_\_

- Durante o fim-de-semana: \_\_\_\_\_

Qual é o tempo total de sono diário da criança? (considerando o sono da noite e as sestas)

\_\_\_\_\_

A criança tem alguma doença conhecida?

Sim

Não

- Se SIM, qual?

Neurofibromatose do tipo 1

Autismo

- Perturbação de Deficit de Atenção com Hiperactividade
- Depressão
- Epilepsia - Há quanto tempo teve a última convulsão? \_\_\_\_\_
- Outra(s) doença(s): \_\_\_\_\_

A criança toma algum medicamento regularmente?

- Sim
- Não

- Se SIM, qual é o nome do(s) medicamento(s) e com que regularidade o(s) toma? \_\_\_\_\_

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Acha que a criança tem algum problema com o sono ou com o adormecer?

- Sim
- Não

A segunda parte do inquérito diz respeito aos hábitos de sono da criança e possíveis problemas com o sono. Para responder às questões, pense no que aconteceu na semana passada. Se o sono foi diferente do habitual nessa semana por alguma razão (por exemplo, por ter estado doente, de férias, etc.), pense noutra semana recente que considere mais normal. Nas perguntas que se seguem, coloque uma cruz na coluna mais apropriada, de acordo com a seguinte chave:

- **Habitualmente**: se o comportamento descrito ocorre **5 ou mais vezes** durante a semana.
- **Às vezes**: se o comportamento ocorre **2 a 4 vezes** durante semana.
- **Raramente**: se o comportamento ocorre apenas **1 vez** durante a semana **ou nunca** acontece.

<b>HORA DE DEITAR</b>			
<b>A criança...</b>	<b>HABITUALMENTE</b> (5 a 7 vezes por semana)	<b>ÀS VEZES</b> (2 a 4 vezes por semana)	<b>RARAMENTE</b> (1 vez ou nunca)
Deita-se sempre à mesma hora	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Depois de se deitar, demora até 20 minutos a adormecer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Adormece sozinha na sua própria cama	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Adormece na cama dos pais ou dos irmãos	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Precisa de um dos pais no quarto para adormecer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
"Luta" na hora de deitar (chora, recusa-se a ficar na cama, etc.)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tem medo de dormir no escuro	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tem medo de dormir sozinha	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

<b>COMPORTAMENTO DURANTE O SONO</b>			
<b>A criança...</b>	<b>HABITUALMENTE</b> (5 - 7 vezes)	<b>ÀS VEZES</b> (2 - 4 vezes)	<b>RARAMENTE</b> (0 - 1 vezes)
Dorme pouco	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dorme o que é necessário	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dorme o mesmo número de horas todos os dias	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Molha a cama à noite (crianças com 4 anos ou mais)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fala a dormir	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tem sono agitado, mexe-se muito a dormir	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Anda a dormir, à noite (sonambulismo)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Vai para a cama dos pais, irmãos, etc., a meio da noite	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Range os dentes durante o sono	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ressona alto	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Parece parar de respirar durante o sono	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ronca ou tem dificuldade em respirar durante o sono	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tem dificuldade em dormir fora de casa (na casa de familiares, nas férias, etc.)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Acorda durante a noite a gritar, a suar, inconsolável	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Acorda assustada com pesadelos	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

<b>ACORDAR DURANTE A NOITE</b>			
<b>A criança...</b>	<b>HABITUALMENTE</b> (5 - 7 vezes)	<b>ÀS VEZES</b> (2 - 4 vezes)	<b>RARAMENTE</b> (0 - 1 vezes)
Acorda uma vez durante a noite	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Acorda mais de uma vez durante a noite	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

<b>ACORDAR DE MANHÃ</b>			
<b>A criança...</b>	<b>HABITUALMENTE</b> (5 - 7 vezes)	<b>ÀS VEZES</b> (2 - 4 vezes)	<b>RARAMENTE</b> (0 - 1 vezes)
De manhã, acorda por si própria	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Acorda mal-humorada	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
De manhã, é acordada pelos pais ou irmãos	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tem dificuldade em sair da cama de manhã	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Demora a ficar bem acordada	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

<b>SONOLÊNCIA DURANTE O DIA</b>			
	<b>HABITUALMENTE</b> (5 - 7 vezes)	<b>ÀS VEZES</b> (2 - 4 vezes)	<b>RARAMENTE</b> (0 - 1 vezes)
Parece cansada	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Na semana passada, a criança pareceu sonolenta em alguma destas situações?</b>	<b>Não ficou sonolenta</b>	<b>Ficou muito sonolenta</b>	<b>Adormeceu</b>
A ver televisão	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
A andar de carro	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Data de preenchimento do questionário: \_\_\_/\_\_\_/\_\_\_

Agradecemos que deixe um contacto, para a eventualidade de surgirem dúvidas relativamente às respostas assinaladas:

Nº de telefone/telemóvel: \_\_\_\_\_

Endereço de e-mail: \_\_\_\_\_

**Muito obrigado pela sua colaboração.**