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TITLE: Longitudinal, Objective Measurement and Analysis of Sleep-Wake Patterns in NF1 Patients

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Sleep disturbances are commonly reported symptom in NF1 patients. Disrupted sleep may contribute to an overall poor quality of life and, additionally, may contribute to the other symptoms of NF1. Studies in NF1 knockout model organisms (mice and fruit flies) suggest that sleep disruption in NF1 may reflect a fundamental role for the neurofibromin protein (encoded by the NF1 gene) in the functioning of the molecular clock which serves to coordinate our internal time (body clock) with the external rhythm (day/night cycle). To date, there have been no true scientific measurements of timing, quantity and quality of sleep in NF1 patients, with previous studies relying upon questionnaires to collect data. This study will address how prevalent sleep disruption is among people with NF1 and define the specific aspects of sleep that are affected. Sleep characteristics will be assessed in a large number (>100) individuals with NF1 and healthy control (>100) subjects, with 18 subjects recruited. This study will be the first to use objective data gathering methods to study sleep in NF1 patients.

15. SUBJECT TERMS
None listed.

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1. INTRODUCTION

Based upon anecdotal reports from patients and family members, clinicians, and previous studies utilizing self-reporting via questionnaires, we hypothesize that sleep disturbance and poor sleep quality are a frequently occurring symptom in individuals with NF1. We hypothesize that since good sleep is critical to overall health, this aspect of NF1 may have a significant impact on the quality of life of patients, as well as potentially contributing to other more well-defined neurological symptoms, such as cognitive or attention deficits. We speculate that the normal function of NF1 may play a role in homeostatic sleep/wake activity or the cell-autonomous circadian rhythm.

Our objective is to define the precise sleep and circadian phenotypes within a cohort of both children adults with NF1. Together, the data sets and analyses in the proposed study will provide new insights into NF1 and sleep. We anticipate that we will generate new hypotheses and opportunities for the NF1 research community to gain a better understanding of the mechanisms involved in NF1 sleep disorders. This study may also impact the clinic by leading to better care and quality of life for patients and possible opportunities for devising interventions and developing novel therapeutic approaches.

2. KEYWORDS

Sleep disturbances, circadian rhythm dysfunction, cognition, neurofibromatosis 1, pain, quality of life, genotype-phenotype relationship, actigraphy

3. ACCOMPLISHMENTS

What were the major goals of the project?

The major goals of the project were to assess sleep and circadian rhythm disturbances in patients with NF1 relative to matched controls. For Specific Aim 1, the major goal was to obtain longitudinal sleep/wake data from NF1 patients and family-based or matched controls. Major Task 1 was Regulatory Approval with two subtasks. Subtask 1 included obtaining Local IRB/HRPO approval in months 1-3. This task took until month 8 to complete, primarily due to COVID-related delays in clinical research and changes to remote consenting of patients. Subtask 2 included preparation of recruitment documents, RedCap Diary, purchase and calibration of actiwatches, patient enrollment and recruitment. We also developed a cognitive battery of tests administered daily and at the beginning and end of the 2 week study period that could be administered online through a web

platform, test my brain.org. This task was completed by month 10, and the milestone of IRB/ HRPO Approval was achieved by month 10 rather than month 5. We then embarked on Major Task 2, which includes ongoing data collection from patients and their controls by month 11. This task is actively ongoing, with components of data collection including wrist actigraphy (subtask 1), implementation of validated sleep and quality of life questionnaires (subtask 2), biobanking (subtask 4), performing online cognitive assessments (subtask 5). Comparison between web-reported and smartphone-based real time reporting of pain, sleep and quality of life (subtask 3) has not yet begun, but is in planning and data analysis (subtask 6) will be completed when all data are collected by month 24. Thus we are now back on track for data collection and data analysis planned in months 12-24 of the grant.

What was accomplished under these goals?

The major activities during this reporting period included establishing and finalizing the research protocol, applying for and obtaining IRB approval from our research institutional ethical research committee, obtaining HRPO approval from the DOD office, and beginning of recruitment of patients for the research study. So far, we have completed research data acquisition on 18 patients with NF1 and controls. Other participants are consented and waiting to begin the studies. To avoid disruptions to sleep and circadian rhythms based on the time change from daylight savings time to eastern standard time, we stopped the study for two weeks before and after the change to allow participants to adjust to the time change.

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

We will continue with Major Task 2 in Specific Aim 1, to obtain longitudinal sleep wake data from NF1 patients and complete the assessment of 100 NF1 patients and 100 matched controls. Assessments will include all subtasks outlined, including actigraphy, diaries, questionnaires, pain, quality of life, cognitive assessments, biobanking of samples, and comparison of web and smartphone-based sleep. Once the recruitment goal is reached and data are collected, data analysis and recontact of a subset of patients for circadian rhythm determination in Aim 2 will be performed.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on society beyond science and technology?

So far, we have begun to assess sleep patterns in NF1 patients and their matched controls, and interest and participation in the study from patients with NF1 has been high. People are eager to learn about the study and in measuring the quality, quantity and timing of their sleep and in practicing good sleep hygiene. Nothing to report for formal impact.

5. CHANGES/PROBLEMS

Changes in approach and reasons for change

Online consent and remote patient sample collection was explored as patients may not have wanted to visit the hospital during the pandemic. This was approved by the IRB/ HRPO.

Actual or anticipated problems or delays and actions or plans to resolve them

Protocol preparation and IRB approval took longer than anticipated, however once the protocol was finalized and approved, recruitment has been extremely effective, so we expact that we will still reach our target recruitment by end of year 2.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects

Nothing to report.

6. PRODUCTS

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATORS

Name:	Richa Saxena
Project Role:	PI
Researcher Identifier (ORCID)	0000-0003-2233-1065
Nearest person month worked:	1
Contribution to Project:	Led study and protocol design, brought together team and coordinated biweekly meetings, oversight of IRB and data collection
Funding Support:	

Name:	Angela Chen
Project Role:	Senior Clinical Research Coordinator
Researcher Identifier (ORCID)	N/A
Nearest person month worked:	3
Contribution to Project:	Prepared and submitted IRB documents, and is leading ongoing subject recruitment and data collection for each participant
Funding Support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

The PI has had changes in active support, as several NIH R01 grants have been completed in 2021, and the PI is now contributing effort as co-investigator to several new grants.

PJP Research Grant 2021 (Gray PI) 01/01/21-12/31/22 0.60CM

Preeclampsia Foundation

Multi-omics for precision medicine in preeclampsia

This project aims to perform statistical analyses on novel molecular phenotypes derived by the TopMed Consortium Boston-Colombia collaborative adverse pregnancy outcome study and other preeclampsia studies

Role: Co-Principal Investigator

R01 HL153969 (Scheer PI) 04/01/21 - 03/31/26 0.60CM

NIH-NHLBI

Food Timing to Mitigate Adverse Consequences of Night Work

The major goals of this project are to determine whether restricting meal timing to the biological day – without disrupting sleep - can mitigate the adverse metabolic effects of circadian misalignment, which may help in the design of evidence-based dietary interventions to improve the metabolic health in shift workers.

Role: Co-Investigator

R01 HL153814-01A1 (Wang PI) 04/01/21 - 03/31/26 0.60CM

NIH-NHLBI

Dissecting heterogeneity of excessive daytime sleepiness and impact on cardiovascular diseases

This work will advance our understanding of the heterogeneity of EDS, reveal biological mechanisms and pathways linking to CVD, and provide information that will guide clinical and public health interventions as well as provide directions for future laboratory research

Role: Co-Investigator

1R01DK127254-01A1 (Czeisler PI) 07/01/21-06/30/26 0.24CM

NIDDK/NIH

Influence of nocturnal light exposure on the impairment of glucose tolerance induced by chronic sleep restriction

This project aims to evaluate the extent to which artificial light at night-induced endocrine and circadian disruption is a primary upstream toxic exposure contributing to the sleep-restriction-induced impairment of glucose metabolism and consequent increase in diabetes risk; genetics will examine interindividual differences in impaired glucose metabolism.

Role: Co-Investigator

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

Nothing to report.

9. APPENDICES

Nothing to report.