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

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CONTRACTING ORGANIZATION: Massachusetts General Hospital

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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 is to obtain longitudinal sleep/wake data from NF1 patients and family-based or age and sex matched population-based controls. This aim includes characterization of sleep and circadian rhythm disturbances in individuals with NF1 using wrist actigraphy, patient questionnaires/surveys to gather more information about each participant’s overall health and mood, real-time reporting of pain and cognitive function, and biobanking of saliva samples for each consenting subject for subsequent NF1 genotyping. For Specific Aim 2, the major goal is to perform overnight sleep and circadian rhythm assessments of patients and controls with extreme patterns.

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What was accomplished under these goals?

We initiated our clinical research study during the first year and have thus far enrolled 40 participants and 12 matched controls. Major Task IRB/HRPO approval was obtained in year 1. Major Task 2 subtasks included preparation of recruitment documents, RedCap Diary, purchase and calibration of actiwatches, development of a 5 min cognitive battery of tests administered daily and a 15-min test 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 ongoing data collection from patients and their controls. This task is actively ongoing, with components of data collection including wrist actigraphy for sleep, activity and light assessment (subtask 1), validated sleep and quality of life questionnaires (subtask 2), biobanking (subtask 4), performing online cognitive assessments (subtask 5). Daily sleep logs include real time reporting of pain, sleep and quality of life (subtask 3). We have also begun data cleaning and draft analysis for Major Tasks 2 and 3. Data analysis (subtask 6) will be completed when all data are collected, however new methods allow assessment of circadian rhythm based on changes in activity during sleep cycles using these same data (Major Task 3 subtask 4). So far, we have completed research data acquisition on 40 patients with NF1 and 12 matched controls. Another ~30 participants are 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?

The project has provided clinical research training for a clinical research coordinator, Angela Chen, who then went on to medical school in Fall 2022. We have also had two full time Northeastern University student interns who have trained in clinical research through this project over the last year.

How were the results disseminated to communities of interest?

Nothing to report. To advertise the study and encourage participation, Jim Walker's lab and our student intern did a presentation of the goals of the research study at the NF1 Summit in Chicago in July 2022. We have also communicated with multiple patient advocate groups (NF1 network, Children Tumor Foundation).

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 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

The COVID-19 pandemic has slowed down the clinical research study. At first, protocol preparation and IRB approval took longer than anticipated but the protocol was finalized and approved in year 1. Over the last year, while recruitment has been extremely effective, staff turnover was high, so we continue to push for target recruitment. We aim to hire both a postdoc and clinical research coordinator to complete recruitment and analyses for the studies.

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:	1.5
Contribution to Project:	Prepared and submitted IRB documents, and is leading ongoing subject recruitment and data collection for each participant. Angela Chen left for medical school this

	summer.
Funding Support:	

Name:	James Walker
Project Role:	Co-I
Researcher Identifier (ORCID)	0000-0001-5585-698X
Nearest person month worked:	1
Contribution to Project:	Led relationship with the NF1 advocacy groups, interviewed personnel, and advised on study recruitment
Funding Support:	

Name:	Michael Parsons
Project Role:	Co-I
Researcher Identifier (ORCID)	N/A
Nearest person month worked:	1
Contribution to Project:	Advised on cognitive assessments, established daily battery of tests for patients and controls using the web platform test my brain. Org and involved in quality assessment of data on ongoing basis
Funding Support:	

Name:	Elizabeth Klerman
Project Role:	Co-I
Researcher Identifier (ORCID)	0000-0002-7402-3171

Nearest person month worked:	1
Contribution to Project:	Selected subjective and objective sleep assessment tools, assisted with actigraphy data
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, and the PI is now contributing effort as PI and co-investigator to several new grants.

R01 HL163234-01 (Saxena PI) 04/01/22 - 03/31/26 2.40CM NIH-NHLBI

Integrative omics of preeclampsia in TOPMed and maternal cardiovascular health

This project aims to discover common and rare variants for preeclampsia, identify molecular pathways altered before clinically defined disease using multi-omics analysis, and use PE polygenic scores to predict maternal morbidity and future maternal cardiovascular health

Role: PI

R01HL146751-03S2 (Saxena, Walker, Melkani PI) 04/01/21 - 03/31/23 0.12CM NIH-NHLBI

Dissecting causal role of insomnia in cardiovascular disease

This Alzheimer's supplement aims to examine genes and pathways at 57 GWAS loci for insomnia symptoms in relation to sleep and Alzheimers disease in humans and in Drosophila.

Role: PI

R01AI170850 (Saxena PI) 08/18/22 - 07/31/27 1.20CM NIH-NIAID

Long COVID as a putative subtype of chronic fatigue syndrome

This grant contributes to our understanding of the underlying and possibly shared genetic risk factors behind Long COVID and CFS and the impact from infectious triggers on disease risk. The findings will elucidate genetic risk factors and enable the development of prevention strategies for CFS and Long COVID.

Role: PI

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

Nothing to report.

9. APPENDICES

Nothing to report.