PLEASE NOTE: *This trial has been registered retrospectively.*

Trial Description

Title

Evaluation of cardiovascular and respiratory autonomic control during sleep and arousal in patients with familial dysautonomia

Trial Acronym

Familial Dysautonomia sleep study

URL of the trial

[---]*

Brief Summary in Lay Language

The purpose of this study is to check how different periods of sleep as well as waking-up may influence heart rate, breathing and blood pressure. All these parameters are functions of the autonomic nervous system (i.e. part of nervous system that controls involuntarily many bodily functions like blood pressure, heart rate, breathing etc.). In Familial Dysautonomia, disturbances of these bodily functions sometimes might lead to severe events, like large rises of blood pressure and heart rate accompanied by vomiting and sweating (such episodes are called dysautonomic crises) or to long pauses in breathing during the night accompanied by falls in blood pressure and heart rate. We plan to see if and how these problems (i.e. dysautonomic crises and pauses in breathing) can be related to changes in the function of autonomic nervous system during sleeping or waking-up.
Through better knowledge of the function of autonomic nervous system during sleep and wakefulness in familial dysautonomia (FD) patients, we hope to gain greater understanding and better treatment of FD patients, resulting in improved quality of life.

Brief Summary in Scientific Language

Familial dysautonomia (FD), i.e. the hereditary sensory and autonomic neuropathy (HSAN) type III, or Riley-Day-Syndrome, is a rare autosomal recessive disorder with extensive central and peripheral autonomic perturbations, accounting for cardio- and cerebrovascular dysregulation as well as compromised respiratory control. Although the prognosis for FD has markedly improved with better treatment, patients with FD still succumb to severe hypertensive dysautonomic crises and sudden unexplained death. Clinically, such events frequently occur during sleep or arousal from sleep, particularly in early morning hours or after having taken a nap. It is still unclear, however, why and how the crises and sudden fatalities are linked to the sleep cycle in FD. Gadoth et al. demonstrated

altered sleep architecture with a decreased amount of REM periods, prolonged REM latencies and an increased number of apneic episodes during sleep in FD patients. However, the authors did not evaluate cardiovascular autonomic function during particular sleep stages. Our group studied cardiovascular responses to apnea evoked by brief hyperventilation in FD and demonstrated a strikingly prolonged duration of the apnea, with marked bradycardia and absent compensatory vasoconstrictor responses. The appropriate response of blood pressure and heart rate to apnea and hypoxia requires an intact interaction between baro- and chemoreflexes. In familial dysautonomia, baroreflex function and the cardiovascular response to baroreflex activation are compromised. In our FD patients, we observed pronounced hypotension and bradycardia without an increase in ventilation during artificially induced hypoxia. These findings indicate that the interaction of the baroreflex and chemoreflex is impaired in FD. Altered chemo- and baroreflex interaction has already been considered a likely cause of sudden infant death syndrome (SIDS) and of sudden deaths in cardiovascular diseases. It seems likely that an altered chemo- and baroreflex interaction is also responsible for sudden fatalities in FD patients.
Normally, baroreflex sensitivity increases during sleep. As baroreflex function is compromised in the FD patients, we assume that apneic episodes in sleep might result in excessive hypotension and bradycardia, potentially leading to asystole and sudden death.
As the decrease in ventilatory control and prolonged sleep apneas of FD patients primarily occur during REM sleep and stage 2 of NREM sleep, we assume that FD patients are particularly prone to develop cardiovascular emergencies with hypotension and unbuffered bradycardia during these sleep stages.
Even in healthy persons, there are brief, marked decelerations of heart rate during REM sleep. In FD patients, this bradycardia in combination with the deficiency of primarily sympathetic cardiovascular innervation and a resulting cardiovagal predominance might induce severe bradyarrhythmias and thus contribute to sudden fatalities.
The clinical observation of an increased occurrence of dysautonomic crises in early morning hours might be explained by autonomic changes occurring during arousal from sleep. These arousal related autonomic changes include centrally mediated transient increases in ventilation, heart rate, blood pressure and muscle-nerve sympathetic activity (MSNA), all indicating a transient, prominent increase in sympathetic tone. Such autonomic changes are similar to physiologic responses described as the "fight-or-flight" response occurring with potentially threatening stimuli. The time relation of the autonomic bursts to the sleep cycle can be identified in the electroencephalogram, as the sympathetic activation is associated with the K-complexes. Since FD patients are particularly susceptible to even moderate emotional or physical stimuli, it seems rather likely that hypertensive crises are triggered by blood pressure surges occurring during NREM phases and during REM sleep and particularly during arousal from sleep.
So far, cardiovascular and respiratory function during particular phases of the sleep and wake cycle has not been studied in FD patients in detail.
The autonomic and sleep related abnormalities so far observed in FD patients, justify the assumption that dysautonomic crises and cardiovascular emergencies are triggered by inadequate autonomic function during distinct phases of the sleep-wakefulness cycle. Sleep apnea, effects of arousal and of transitions from NREM stages to the REM sleep might elicit dysautonomic crises and cardiovascular emergencies.
Therefore, we hypothesize that inadequate responses to autonomic changes occurring during sleep and arousal phases are a major cause of life threatening cardiovascular emergencies in FD patients.
We assume that a detailed evaluation of cardiovascular autonomic function during sleep and wakefulness will better elucidate the mechanisms of cardiovascular

emergencies in familial dysautonomia and will possibly allow for therapeutical interventions mitigating some of the sleep related cardiovascular instability in FD patients.

Organizational Data

- DRKS-ID: **DRKS00008852**
- Date of Registration in DRKS: **2015/07/01**
- Date of Registration in Partner Registry or other Primary Registry: **[---]***
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **11051 , Institutional Review Board**
  New York University School of Medicine
  New York University Langone Medical Center
  1 Park Avenue, 6th Floor
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  USA

Secondary IDs

Health condition or Problem studied

- Free text: **Familial Dysautonomia**
- ICD10: **G90.1 - Familial dysautonomia [Riley-Day]**
- Free text: **Healthy Volunteers**

Interventions/Observational Groups

- Arm 1: **patients with Familial Dysautonomia -**
  polysomnographic recordings of EEG, EOG, EMG, ECG, blood pressure, breathing frequency, Oxygen-saturation, periodic leg movements, end-expiratory carbon dioxide (CO2) and air flow during one night, filling out a questionnaire "Pittsburgh Sleep Quality Index"
- Arm 2: **healthy participants -**
  polysomnographic recordings of EEG, EOG, EMG, ECG, blood pressure, breathing frequency, Oxygen-saturation, periodic leg movements, end-expiratory carbon dioxide (CO2) and air flow during one night, filling out a questionnaire "Pittsburgh Sleep Quality Index"

Characteristics

- Study Type: **Non-interventional**
- Study Type Non-Interventional: **Other**
- Allocation: **Non-randomized controlled trial**
- Blinding: **[---]***
- Who is blinded: **[---]***
- Control: **Active control (effective treament of control group)**
- Purpose: **Diagnostic**
- Assignment: **Parallel**
- Phase: **N/A**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **N/A**

Primary Outcome

For this study, no end-points were defined. Aim of the study is to identify autonomic and respiratory disturbances during specific sleep or arousal stages in patients with Familial Dysautonomia.
Using a portable polysomnograph, we will continuously monitor the following signals for 12-16 hours:
- the electrocardiogram (ECG) using conventional superficial disc electrodes attached to the area under the right and left clavicles and the right and left lower thorax,
- electrooculogram (EOG),
- electroencephalogram (EEG) at the standard scalp positions of the international 10-20 system using superficial disc electrodes,
- electromyography (EMG) using surface electrodes placed laterally to the chin, body position using a polysomnograph unit integrated sensor,
- periodic leg movements (PLM) using 3-point EMG electrodes placed over left and right anterior tibial muscle,
- oxygen (O2) saturation by means of finger pulsoxymetry,
- end-expiratory carbon dioxide (CO2) and air flow using nasal cannulas, and
- respiration by means of plethysmographic belts attached to the lower thorax and around the mid-abdomen, at the points of maximal respiratory excursion.
- In addition, we will measure blood pressure continuously by means of non-invasive infrared finger plethysmography.
After 12-16 hours, the equipment will be removed and data downloaded to a personal computer. The data will be cleaned from artefacts and further analyzed. Particular sleep stages and arousals will be differentiated by means of EEG, EOG, EMG and respiration.
The other parameters will be used to evaluate the autonomic nervous system. Moreover, we will ask the participants to fill out the sleep questionnaire "Pittsburgh Sleep Quality Index". The "Pittsburgh Sleep Quality Index" evaluates the sleep quality during the previous month.

Secondary Outcome

For this study, no secondary end-points were defined.

Countries of recruitment

- US **United States**

Locations of Recruitment

Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2004/10/28**
- Target Sample Size: **60**
- Monocenter/Multicenter trial: **Monocenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **10 Years**
- Maximum Age: **no maximum age**

Additional Inclusion Criteria

All FD patients have to have the characteristic genetic haplotype, i.e. they have to be homozygous for the intron 20 mutation on the IKBKAP gene and need to fulfill the diagnostic criteria of FD including Ashkenazi Jewish ancestry, absence of deep tendon reflexes, overflow tears, lingual fungiform papillae, and of axon flare response following intradermal histamine injection. Only mildly affected FD patients without significant, clinically overt respiratory difficulties will participate in the study.

Exclusion criteria

a. If the patient's body weight is less than 25 lbs.

b. Age < 10 years

c. If the patient is acutely ill or manifesting signs of dysautonomic crisis

d. If the core (oral) temperature is > 38°C

e. If the patient has acute respiratory compromise, i.e. pneumonia

f. If the patient has severe chronic lung disease as judged by an oxygen saturation <95% supine

g. Bradycardia, second-degree AV block, complete AV block, sick sinus

syndrome,
chronic heart failure assessed as NYHA class IV

h.If the patient is on nocturnal oxygen supply

i. If the patient requires overnight gastrostomy feeding

Addresses

- **Primary Sponsor**

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Sources of Monetary or Material Support

- **Private sponsorship (foundations, study societies, etc.)**

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Status

- Recruitment Status: **Recruiting complete, follow-up complete**
- Study Closing (LPLV): **2005/07/15**

Trial Publications, Results and other documents