Treatments of Mal de Debarquement Syndrome (MdDS) by Habituation of Velocity Storage
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RESEARCH PROTOCOL

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Project Title: Treatment of Mal de Debarquement Syndrome (MdDS) by habituation of Velocity Storage

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Brief Summary of Research:

Mal de Debarquement Syndrome (MdDS) is an under-recognized balance disorder, which in most cases occurs after exposure to prolonged passive motion (a cruise). MdDS is manifested by constant postural rocking and/or swaying and the body's gravitational pull. It is accompanied by high sensitivity to light, noise, crowds, cognitive dysfunctions (thinking challenges), including short-term memory loss. In addition to motion-triggered (MT) MdDS, similar symptoms also occur without a clear trigger, identified as spontaneous MdDS. Recently, we developed an effective treatment method for MdDS based on the readaptation of the vestibulo-ocular reflex (VOR). The hypothesis underlying this treatment is that MdDS is caused by maladaptation of a functional component of the VOR called velocity storage, whose readaptation can be stimulated by exposure to whole-field visual motion. Our current success rate immediately after treatment of MT MdDS is 75%. However, some patients report symptoms returns after flights or prolonged car rides following a treatment. Thus, for some patients, the effectiveness of the current MdDS treatment appears to depend on a serious practical limitation of needing to permanently avoid transportation. Building on the previous hypothesis of velocity storage maladaptation, we currently hypothesize that reduction (habituation) of velocity storage can also resolve MdDS symptoms. Velocity storage can be significantly habituated by 4-5 days of treatment with a protocol previously designed in our laboratory to reduce susceptibility to motion sickness. Preliminary data support that velocity storage habituation reduces MdDS symptoms. In this project, 30 MT MdDS patients with no history of inner ear problems and no severe neurological decoders will be randomly assigned into two groups. Group 1 will be treated with the habituation protocol only, and Group 2 will be treated with the VOR readaptation protocol only. Patients will be followed up for up to 6 months. Based on the preliminary data, we expect both groups to experience similar initial symptom improvement, but the group undergoing the habituation protocol will potentially retain the initial treatment impact. This project hopes to broaden treatment options for MdDS and increase the current understanding of recurrent MdDS.

Background

While MdDS has been known for centuries (Darwin 1796), until 2014, there was no effective treatment available (Dai et al., 2014). Benzodiazepines have a partial positive effect on MdDS symptoms, but only in a small group of patients (Cha, 2012; Hain et al., 1999), and harmful effects including dependence (Nutt et al., 2007) must also be considered. The readaptation method was invented by Dr. Dai and colleagues at Mount Sinai (Dai et al., 2014). The effectiveness of the readaptation treatment method was independently confirmed by others (Schenk et al., 2018), and a sham-controlled study was performed to further assess the readaptation protocol (Mucci et al., 2018).

Since velocity storage integrator was first described in the 1970s (Raphan et al., 1977; Robinson, 1977), it remained mostly purely a research topic with little clinical implications. Only in the last decade here at Mount Sinai was it shown by Dr. Dai and colleagues that the activity of the velocity storage integrator is responsible for motion sickness (Dai et al., 2011). Subsequently, it was suggested that adaptive changes in velocity storage are the basis of MdDS (Dai et al., 2014, 2017). In the current project, we will provide a clinical assessment of this hypothesis.

Objectives

Mal de Debarquement Syndrome (MdDS) is an under-recognized balance disorder, which in most cases occurs after exposure to prolonged passive motion. MdDS is manifested by constant postural rocking and/or swaying and by the gravitational pull of the body. It is accompanied by high sensitivity to light, noise, crowds, cognitive dysfunctions, including short-term memory loss. Recently, we developed an effective treatment method for MdDS based on the readaptation of the vestibulo-ocular reflex (VOR). The hypothesis underlying this treatment is that MdDS is caused by maladaptation of a functional component of the VOR called velocity storage, whose readaptation can be stimulated by exposure to whole-field visual motion. Our current success rate immediately after treatment of MT MdDS is 75%. However, some patients report symptoms returns after flights or prolonged car rides following a treatment. Thus, for some patients, the effectiveness of the current MdDS treatment protocol appears to depend on a serious practical limitation of needing to permanently avoid transportation. Building on the previous hypothesis of velocity storage maladaptation, we currently hypothesize that reduction (habituation) of velocity storage can also resolve MdDS symptoms. Velocity storage can be significantly habituated by 4-5 days of treatment with a protocol previously designed in our laboratory to reduce susceptibility to motion sickness.

Specific Aims

The goal of this project is to establish a new effective treatment protocol for Mal de Debarquement Syndrome (MdDS), which not only reduces patients' symptoms but also works in the long term by reducing their susceptibility to recurrent MdDS due to re-exposure to passive motion. This new protocol is expected to liberate treated patients from the possible need to permanently steer away from traveling.

The previously established MdDS treatment protocol is via readaptation of the vestibulo-ocular reflex (VOR), in particular a functional component of the VOR known as velocity storage. Building on the hypothesis of velocity storage maladaptation as the neural basis of MdDS, we currently hypothesize that velocity storage habituation can also resolve MdDS symptoms by minimizing the contribution of the maladapted component of the VOR. The effectiveness of MdDS treatment by the habituation and readaptation protocols will be compared through two Specific Aims.

Specific Aim 1: Assess the efficacy of MdDS treatment via habituation of velocity storage. It was previously demonstrated that the contribution of velocity storage to the VOR could be eliminated by a habituation protocol. Fifteen MT MdDS patients with no peripheral vestibular abnormalities (Group 1) will undergo this protocol over the period of four days. Objective and subjective symptoms will be assessed with a standardized test battery (**Methods 1**) before and after habituation.

Specific Aim 2: Further assess the efficacy of MdDS treatment via VOR readaptation and compare success rate with Group 1, which underwent the habituation protocol. Fifteen MT MdDS patients with no peripheral vestibular abnormalities (Group 2) will undergo the VOR readaptation protocol over the period of four days. Objective and subjective symptoms will be assessed with a standardized test battery before and after readaptation. Treatment effectiveness will be compared between the two groups immediately and 6 months after treatment.

Number of subjects

Subjects To Be Enrolled 60

Study Timelines
We planning to recruit all 60 patients by August 2022.

Duration Anticipated to Enroll All Study Subjects
18 months

Estimated Date for the Investigators to complete this study
Within 3-5 years

Setting of the Human Research
How Participants Will Be Identified
Vestibular Testing Center at Mount Sinai has treated 3-7 patients with MdDS on a weekly basis, receiving 3-15 applications for treatment per week. The treatment is advertised on web sites of Mount Sinai and Vestibular Testing Center (www.mdds.nyc). We anticipate reaching out to all previously treated MdDS patients who are part of the Vestibular Testing Center's clinical database to offer the study. The study treatment provider (Dr. Yakushin, PI) will mail or email the letter discusses the study and the ability for the participant to 'opt out' of being contacted concerning the study.

How Research Will Be Introduced to Participants
Potential subjects will be interviewed over the telephone for confirmation and clarification of their MdDS symptoms. Once the participant potentially meets the entry criteria, they will be consented over the phone following the HRP 093 policy are scheduled for a screening visit or a screening telephone call.

How Participants Will Be Screened
Participants will be consented at a distance (HRP 093) and then review their MdDS and general medical history and complete an intake form that asks questions regarding the history of MdDS and general medical history. If there are further questions about the MdDS they will be referred for a telephone screening with Dr. Catherine Cho at NYU to confirm eligibility. Dr. Cho is having the protocol reviewed by the NYU IRB to provide approval of this process. Once the entry criteria is confirmed, the participant will be scheduled for an in-person appointment where the written component of the consent form will be completed. At this visit the participant will be randomized, and the subject can begin the first study treatment.

Study Design
a) Recruitment Methods
Since August 2014, Human Balance Laboratory at Mount Sinai has treated 3 to 7 patients with MdDS on a weekly basis, receiving 3 to15 applications for treatment per week. The treatment is advertised on web sites of Mount Sinai and Human Balance Laboratory (www.mdds.nyc). Former patients also promote the treatment through MdDS support groups on yahoo and Facebook. Referrals from medical doctors are also considered. In total, over the last 4 years, we received more than 1,500 requests and treated about 700 patients with MdDS, of whom 135 were local residents, and 90% were aged 20-70 years old. Only 7 of the 135 patients had low symptoms (Score <4) prior to the treatment. We expect intake trends to be similar or increase in the coming years. Potential subjects will first complete a patient intake form with questions regarding the history of MdDS and general medical history. They will be then interviewed as described above for confirmation and clarification of their MdDS symptoms. Prospective subjects who have more than moderate MdDS without clinically significant central vestibular lesion (normal saccades, normal pursuit, VOR suppression index >85%, presence of caloric response), will be included. On their laboratory visit, the written consent will be completed, and the investigator will verify their history again and explain the procedures involved. Because the majority of MdDS sufferers are women, we expect a gender bias in recruited subjects. Patients of ages 3-78 years old will be randomly assigned to one of two experimental groups. Patients outside this age range

will be excluded due to difficulties matching ages between the two groups. Patients with a history of leg, spine, or other injuries that affect their ability to walk will also be excluded since the reduced walking ability is one of the MdDS symptoms.

b) Other Aspects that Could Increase Subjects Vulnerability

Subjects that have a diagnosis of MdDS include a broad spectrum of the population. More women than men are typically diagnosed with MdDS. Those participants who are socially or economically capable of participating will be included without prejudice.

Otherwise, no other vulnerable populations will be included, specifically no: adults unable to consent, individuals who are not yet adults (e.g., infants, children, teenagers), wards of the state (e.g., foster children), prisoners.

c) Safeguards to protect Subjects rights and welfare

In recruiting subjects, consideration must be given to a person's desire to control how and with whom they interact and communicate. Care to respect the participants' privacy will be taken into consideration in all study activities and all subsequent communications. No specific information will ever be left with family members or in voice messages.

Procedures Involved in the Human Research

d) Inclusion and Exclusion Criteria

Inclusion

1) age 18 – 78
2) Report of the following symptoms: sensation of oscillatory vertigo (rocking, swaying, bobbing, walking on a trampoline, gravitational pull) symptoms started after prolong transportation or spontaneously; symptoms temporarily relieved during passive transportation; Symptoms present when laying down, sitting, and standing positions
3) Capable of signing the informed consent
4) Stay within an hour of the treatment center

Exclusion Criteria

1) Abnormal Vestibular Nystagmography (VNG) test at screening, indicating central vestibular damage.
2) Other confounding neurological disorders (e.g., multiple sclerosis, Parkinson's etc. head trauma)
3) A history of leg, spine, or other injuries that affect their ability to walk will also be excluded
4) Intervention would be harmful
5) Blindness
6) Epileptic diagnosis

Description of Procedures Being Performed

Description of the Study Design

Randomly selected MdDS patient volunteers will be treated with the velocity storage habituation protocol (Group 1, Aim 1). Another group of randomly selected patients of Group 2 will be treated with readaptation of VOR. Before and after the treatment, the severity of the objective and subjective symptoms will be assessed. Indices of postural stability (Method 1) and time constant of velocity storage (Method 2) will be obtained as objective measures. Treatment will take place over four days. The severity of subjective symptoms will be assessed by a self-reported scale of 0-10, where 0 is no symptom, and 10 is the most difficult sensation of that symptom that the patient can imagine. Among these symptoms are brain fog, head pressure, the fullness of the ear, heavy head, headache, nausea, blurry vision, fatigue, sensitivity to fluorescent lights, scrolling of computer screen, sensitivity to noise, walking on a trampoline, the sensation of

gravitational pull-up or down. The visual disturbance will be determined by the Visual Vertigo Analogue Scale and Situational Vertigo Questionnaire. Physical, emotional, and functional aspects of disability related to MdDS will be obtained by Dizziness Handicap Inventory (DHI). The patient will undergo follow-up testing for objective and subjective symptoms at 2 weeks, 1 month, 3 months, and 6 months after the treatment.

Treatment will be considered effective if objective and subjective symptoms are improved at least 50%. The effectiveness of the two treatments would be compared immediately after treatment and up to one year of follow-up phone calls.

Description of Procedures Being Performed

Aim 1: Velocity storage habituation protocol: The central vestibular (velocity storage) time constant will be habituated (reduced) by inducing cancellation of two velocity storage-mediated responses: optokinetic nystagmus (OKN) and the vestibulo-ocular reflex (VOR). The stimulus velocity and the frequency must be low to activate the response characteristics of velocity storage. Low-frequency rotation in darkness advances the phase of the slow phase eye velocity of the induced nystagmus. In normal subjects, the VOR during oscillation at 0.017 Hz has a phase advance of 32º relative to the stimulus and a gain of 0.68 on average. In contrast, the OKN induced by low-frequency optokinetic stimuli has no phase advancement in the slow phase eye velocity. Thus, to counteract the VOR by OKN, the optokinetic stimulus should be set to be 180º out of phase with the expected VOR. Across all subjects, we will use a gain of 0.68 and a phase advance of 30° to generate the optokinetic stimulus relative to the velocity of the chair in which the subject is seated. The optokinetic stimulus occupying the entire visual field is a powerful stimulus, and subjects will not to particularly attentive to the moving stripes to experience the visual motion. Chair velocities will be up to 40°/s. The conflict stimulus is expected to be overwhelming to the patients depending on the stimulus velocities. Subjects will be first tested with a 10°/s stimulus. If they feel uncomfortable, the chair velocity will be reduced to 5°/s or 2°/s and increased gradually. From previous studies, no complaints were reported when subjects were tested at low velocities (Dai et al., 2011). In our preliminary testing, MdDS patients began to show signs of symptom improvement when the peak velocity reached 30°/s. In total, three habituation sessions will be administered each day over the four-day period. Two consecutive sessions with identical stimulus parameters, each lasting 20 min, will be administered with a 10 min break. Then the third session will be administered with an increase in the chair velocity by up to 10°/s. If signs of motion sickness are reported by the subject (nausea, sweating) session will be terminated. Thus, some subjects may not be able to complete the entire 20 min of the intensified stimulus. Therefore, the subjects are expected to undergo 200-280 min of habituation over the 4-5 day period. Eye movements will not be recorded during the habituation training.

Aim 2: Readaptation of the VOR: According to readaptation hypotheses, oscillatory body motion of MdDS patients is a result of adaptive changes in the velocity storage pathway of the VOR induces by prolonging traveling. Symptoms could be reduced by providing new learning that is the opposite to one that occurred during traveling. During treatment, the patient sits in the Barany chair. Optokinetic nystagmus (OKN) will be induced at 5°/s, while the head is oscillated manually by the researcher standing behind the subject.

Determining the direction of OKN. If the patient has spontaneous nystagmus while sitting stationary in darkness, OKN will go in the direction of a quick phase. The patient will also have to perform a Fukuda stepping test (Patient marching in place with eye closes). If the Fukuda step test results in changes of body orientation #20º, over 20 steps, the OKN will be set to start in the opposite direction of the Fukuda deviation. Suppose both tests are negative, but the patient reports circular body motion or sideway directed gravitational pull. In that case, stripes will go in the opposite direction or the main sensation reported by the patient. If the body is stationary but experiences internal sensations, then stripes should go in the same direction. If the patient reports uncomfortable sensation even at low brightness at any time, then the stripes direction will be reversed. If the patient has no history of ocular migraine, the brightness would be set to maximal (3 lux); otherwise, the first treatment started with the brightness of 1 lux. If the patient report that ightness is too high, next time it will be set to 0.3 lux. Some patients report only a gravitational pull with no

rocking, swaying, bobbing, or trampoline walking. In this case direction of the stripe would be opposite to the pulling direction (e.g., right if pulling to the left, left if pulling to the right, down if pulling forward, and upward if pulling backward).

Determining parameters of head motion: The patient assessed will be asked to stand on the Wii board for one min. Some patients experience only internal sensations of rocking. For this reason, a wireless 3D accelerometer will be attached to their wrist. The patient will be asked to move the hand to imitate the internal sensation of motion. Data on body deviations about the center of mass or wrist motion will be recorded with a laptop computer at 1kHz. Traces are visually examined. If oscillations larger than ±10 mm are observed, the frequency of oscillation is determined by fast Fourier transforms. If the body (or internal sensation) is rocking (Forward-back motion), then the head would be rolled during treatment. If the body is swaying, then the head will be pitched.

The first treatment will last 1 min. If improvement is reported, then treatment will be repeated for 1-2 min. We will also test if lower frequencies of head oscillation are effective. The typical set of treatments at lower frequencies includes oscillation at 0.1 Hz for 3 min and at 0.05 Hz for 5 min. The amplitude of head oscillation would be about ±20°.

Description of the Source Records that Will Be Used to Collect Data About Subjects

Objective measure description:

Method 1: Determining postural stability: Static posturography would be obtained with a specifically designed program for a Wii board. The displacement of the center of pressure (COP) over a 1 min period will be measured, and the root means square (RMS) of the postural displacement would be computed (30) to compare the postural stability before and after the treatment. The total trajectory length (maximum excursion) of the COP deviation will be computed over 20 seconds.

Postural stability would be obtained in different conditions:

1) subject will have eye open feet 30 cm apart,
2) subject will be placed under strong fluorescent light and feet open,
3) subject will have an eye open under non-fluorescent light on,
4) subject will be tested with eye closed,
5) subject will be tested with eye open in a small closet (0.9x0.6 m) with extreme dim light,
6) subject will be assessed facing crowded shelves and in a narrow engineering room facing crowded shelves (5x0.91 m).

Body bobbing would be measured by an accelerometer attached to the arm wrist. The patient would be asked to move their wrist up-down to imitate the internal sensation of bobbing. The presence of gravitational pull in sideways, forward or backward directions will be objectively measured with static posturography.

Method 2: 2. Determining Time constant of velocity storage: Subject sits in a standard Barany chair in darkness. This device is commonly used for Vestibular Nystagmography (VNG) testing in clinics all over the world and at Neurology Department at Mount Sinai over the last 30 years. The time constant (Tc) will be determined from rotations at a constant velocity of 60°/s (200°/s^2) in clockwise and counterclockwise directions in darkness. After 60 s, when the per-rotatory VOR has decayed, a laser spot at eye level rotating with the subjects for 10 s will be used to suppress any residual VOR response. After the laser light is turned off, the chair will stop with the same acceleration rate to produce a post-rotatory VOR. 60 s later; the laser light will be displayed to suppress the residual VOR again. Rotatory and post rotatory nystagmus will be recorded. During the test, subjects will perform mental arithmetic, such as multiplication or division problems, arouse their alertness. Movements of the right eye will be recorded with a Video Oculography recording

system (VOG, ISCAN) at a rate of 60 frames/s. Data acquisition will be made through a LabView program at 600 Hz/s/channel. The data will then be transferred to the VMF data management software for further processing. Eye position data from the VOG will be digitally differentiated to obtain eye velocity. Quick phases will be removed, leaving slow phase eye velocity for analyses (Engelken and Stevens 1990). Slow phase velocity traces will be fitted with two Tc's fitting algorithm, where the first Tc is fixed to 5 s (copular Tc) and the second need to be determined (Tc of velocity storage). This algorithm is now embedded in our standard VNG testing protocol.

Subjective measure description: Strength of subjective symptoms will be obtained with subjective self-score on a scale of 0-10, where 0 is no symptom, and 10 is the highest sensation of that symptom that the patient could imagine. Among these symptoms are brain fog, head pressure, the fullness of the ear, heavy head, headache, nausea, blurry vision, fatigue, sensitivity to fluorescent lights, scrolling of computer screen, sensitivity to smell, sensitivity to noise, walking on a trampoline, the sensation of gravitational pull-up or down. The Visual Vertigo Analogue Scale will determine the visual disturbance. Physical, emotional, and functional aspects of disability related to MdDS would be obtained by Dizziness Handicap Inventory (DHI).

Description of Data that Will Be Collected Including Long-Term Follow-Up

Prior to the treatment standard, a VNG test will be performed to determine any significant vestibular abnormality. That includes rotational and caloric tests. Patients with significant central abnormalities will be rejected from this study (see Recruitment method). If the patient has a VNG report done after the onset of MdDS, the only rotational test will be performed to obtain the time constant of VOR (velocity storage). The rotational test will be repeated at the end of the treatment (see Method 2 above). During the rotational test, horizontal and vertical components of eye position in response to chair rotation will be collected for 2 min. The test will be repeated 3 times for statistical purposes. Data in VMF-format will be collected and stored in a computer folder with the patient's ID number.

Prior to and during treatment, static posturography will be performed (Method 1). COP oscillation about X- (forward-back) any Y-axis (side-to-side) will be collected. Data in VMF-format will be collected and stored in a computer folder with the patient's ID number.

Subjective measure description: Strength of subjective symptoms will be obtained with subjective self-score on a scale of 0-10, where 0 is no symptom, and 10 is the hardest sensation of that symptom that the patient could imagine. Among these symptoms are brain fog, head pressure, the fullness of the ear, heavy head, headache, nausea, blurry vision, fatigue, sensitivity to fluorescent lights, scrolling of computer screen, sensitivity to smell, sensitivity to noise, walking on a trampoline, the sensation of gravitational pull-up or down. The visual disturbance will be determined Visual Vertigo Analogue Scale. Physical, emotional, and functional aspects of disability related to MdDS would be obtained by Dizziness Handicap Inventory (DHI). Spreadsheets and paper tables with data will be collected and locked in cabinets. Excel file with the patient's ID will be stored on the computer.

Data Management and Confidentiality

Specimen Banking

N/A

Provisions to Monitor the Data to Ensure the Safety of Subjects

All identifiable information on paper will be locked in a cabinet inside the locked PI office. Individual code will be given to each patient. The remaining data will be stored on a PI computer that is connected with the Mount Sinai system. The participant will have an assigned code, and the linked document is only accessible / PI. The file is password protected.

Only the study team has access to the area where the cabinet is locked; the office is locked. The office has access to the hallway through room 05, which is also locked. Any data stored on the computer is done with password protection and maintained on a Sinai drive that is encrypted.

Withdrawal of Subjects

Subjects can withdraw from this study at any time.

Risks to Subjects

Prolong exposure to visual stimuli can cause headaches. If that happened, it is recommended to take any over counter headache medicine.

Provisions for Research Related Harm/Injury

If the participant experiences a Research Related Harm or Injury they will be referred to treatment but the expense will be the responsibility of the participant or billed to their insurance.

Description of Procedures Taken to Lessen the Probability or Magnitude of Risks

The brightness of the optokinetic stimuli can vary from 3 to 1 lux. If the patient feels uncomfortable watching stripes at 3 lux, brightness will be decreased to a comfortable level.

Provisions for Research Related Harm / Injury

N/A. None

Expected Direct Benefit to Subjects

Symptoms on MdDS could be relieved or significantly reduced.

Benefit to Society

While MdDS is a rare disease, readaptation of the vestibulo-ocular reflex is the only effective method of treatment (75% success rate). In this study, we will test a new method of MdDS treatment and potentially increase the effectiveness of the existing method.

Provisions to Protect the Privacy Interests of Subjects

A unique identification number will be assigned to each enrolled subject. The identification log will be stored separately. All collected digital data (posture, eye movements) will be stored in the directories with the subject's ID. All forms and scoresheets have only subject ID and no identifiable information. All study activities are conducted in a private exam room. All telephone conversations or email will be done in a manner agreed upon by the participant prior to starting the study.

Economic Impact on Subjects

Subjects will have all study activities covered by the research. No payment is being offered for participation

Results of the Study

In this study, we compare the effectiveness of a new method of MdDS treatment to a previously developed method in our lab called the readaptation treatment. Results will be published and presented in peer reviewed journals and conferences. These publications will be shared with participants by email if they wish further information. Also, any participant who wants to receive the same or alternative treatment after completing the follow up can do so clinically.