Study Protocol

Title: Non-invasive Vagus Nerve Stimulation (nVNS) in Pediatric Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

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Study Personnel:

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- Robert Butera, PhD, Georgia Tech, PI

I. Background and Purpose

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a chronic immune-mediated disease of the peripheral sensory motor nerves characterized by motor weakness, sensory loss, muscle wasting and loss of motor ability. Majority of CIDP cases are idiopathic with insidious onset, relapsing remitting course and prolonged (over years) clinical course. CIDP incidence is unknown in pediatric population however it is a rare treatable cause of neuromuscular weakness in children. Treatment of CIDP involves chronic use of steroids, intravenous immunoglobulin (IVIG) and rarely plasma exchange (PLEX). Outcome measures such as patient reported motor disability scores, electrophysiology parameters, functional motor strength testing are available to look for interval change. Despite above mentioned treatments majority of patients have tremendous disease burden. There is a need for alternative/adjunctive therapies that can decrease chronic inflammation effectively and safely in pediatric CIDP patients.

Vagus nerve stimulation has received significant scientific and clinical attention and has been shown to effectively reduce systemic inflammation. Results from early clinical trials for treatment of Rheumatoid Arthritis (NCT01552538, NCT01552941, ClinicalTrials.gov) have demonstrated significant lifestyle benefits and reduced symptoms in RA patients. Similar benefits of VNS have been observed in Crohn's patients (NCT02311660). In these studies, patients are surgically implanted with a stimulator and electrodes directly on the nerve. Preliminary results have demonstrated safety and efficacy in patients that previously were unresponsive to traditional pharmacological therapies. Unfortunately, surgical implantation of a device is difficult and costly.

Recent investigations have significantly increased our understanding of nVNS. Compared to traditional implanted vagus nerve stimulation devices, nVNS uses electrodes placed on the skin surface to stimulate the vagus nerve. Non-invasive vagus nerve stimulation (nVNS) has shown promise in animal and human models to reduce chronic inflammation in multiple disease states. By delivering electrical pulses at the skin surface above the vagus nerve, neural pathways involved in regulating systemic inflammation are activated. Using a handheld device, patients apply brief durations of stimulation multiple times per day to achieve therapeutic benefit. nVNS is currently FDA approved for clinical use in the treatment of migraines and cluster headaches, with on-going clinical studies on epilepsy and systemic inflammation. Preliminary published results have demonstrated significant therapeutic benefit to the patients with minimal side-effects such as a feeling of paresthesia at the site of the electrodes which subsides after turning the

stimulation off.

Hypotheses

We hypothesize that nVNS therapy can reduce systemic inflammation in CIPD patients, functionally halting degradation of motor nerve conduction and hand grip strength.

The specific aims of this proposal are to:

1. Quantify functional changes in motor nerve conduction studies, hand held grip strength, and Rash-built Overall Disability Scale (R-ODS) in CIDP patients receiving standard of care treatment and daily nVNS.
2. Characterize changes in serum cytokine profiles in patients receiving standard of care treatment and daily nVNS.

We anticipate observing a reduction in serum TNF-α levels after nVNS therapy, consistent with previously published clinical results. Serum cytokine levels will be statistically analyzed on a per patient basis, with each patient's baseline measurements used for comparison. will be used to determine statistically significant differences between subsequent serum cytokine profiles for the entire patient population and NCS metrics. Pearson's correlation coefficient will be used to understand the relationship between changes in serum cytokine levels and NCS metrics. Pearson's correlation coefficient will also be used to assess the relationship between number of therapy session (as reported by the patient) and serum cytokine levels.

II. Summary of Procedures

All proposed studies will be conducted at Children's Healthcare of Atlanta (Atlanta, GA) for a total duration of 24 months. Local institution review board approval would be obtained prior to the study. The table below (Table 1) provides an overview of the timeline and specific tasks to be completed upon each visit. Baseline represents the initial visit after the patient has been screened and meets the inclusion criteria (EKG results may take 24-48 hrs and study participant will be advised to start the study intervention once confirmation of normal EKG is obtained) Patients will be scheduled to visit the clinic for follow up visits at the pre-set time points shown. A total of 15 subjects, from age 5 years to 21 years, will be included in the study. The stimulation devices used in this study are VitalStim 400, electrical neuromuscular stimulators, which have been used in multiple previous clinical studies for modulation of pain and have received FDA approval. The (2) electrodes for the device will be placed on the subjects left cervical (neck) region. The stimulator will be placed in a comfortable position, such as next to the pillow. The stimulators are battery-powered and allow configuration of the stimulation parameters to the comfort of the patient.

Parents will be trained on where to place electrodes, how to ensure that the electrodes make a good contact with the skin, and how to set the stimulation parameters.

SCHEDULE of Events

STUDY PROCEDURES (*experimental procedure)	Baseline	3 mon	6 mon	9 mon	12 mon	15 mon	18 mon	21 mon	24 mon
Informed consent	X								
Inclusion/exclusion criteria	X								
Medical history	X	X	X	X	X	X	X	X	X
***nVNS 2 times daily x 60 mins each (log book maintained and reviewed)**	X	X	X	X	X	X	X	X	X
Physical and neurological examination	X		X		X		X		X
Vital Signs	X		X		X		X		X
Cytokine profile	X		X		X		X		X
EKG	X		X		X		X		X
R-ODS scale and handheld dynamometer	X		X		X		X		X
Nerve conduction study	X				X				X
Adverse events	x	X	X	X	X	X	X	X	X
Concomitant medications (IVIG, steroids, PLEX)	X	X	X	X	X	X	X	X	X
Telephone visit/ check (To limit inperson visits due to COVID-19 pandemic)		X		X		X		X	

Table 1. Study outline for nVNS in CIDP patients. Patients will be followed for two years with nVNS as an adjunctive to standard IVIG therapy. Patients will be validated against the stated inclusion criteria prior to enrollment in the study. Baseline measurements before nVNS is added will be taken to determine change in physiological and functional outcomes over time. All procedures other than in-home vagus nerve stimulator therapy will take place at CHOA under the direct guidance of the PI. Parents will be trained on where to place electrodes, how to ensure that the electrodes make a good contact with the skin, and how to set the stimulation parameters. Patient is not required to have anyone sit with them during the stimulation procedure. At the end of two years, we will understand the benefits (or not) of nVNS in CIDP and the compliance of nVNS therapies in pediatric patients.

Specific Aim 1: Quantify functional changes in motor nerve conduction studies, hand held grip strength, and Rasch-built Overall Disability Scale (R-ODS) in CIDP patients receiving standard of care treatment and daily nVNS.

- **nVNS Therapy.** The nVNS therapy will be delivered using a handheld electrical neuromuscular stimulator

(VitalStim 400) device. It is safe, effective at stimulating the vagus nerve, and easy to use by patients outside the clinic. Electrical neuromuscular stimulator devices have been used for years in pain-related preclinical and clinical research. Patients will be requested to deliver nVNS 2 times per day for 60 minutes each time for at least 5 days per week. The stimulation frequency (number of pulses) and amplitude (amount of current) will be set during the initial baseline session in the clinic and will be set to prevent discomfort to the patient or impact cardiorespiratory parameters. Initial stimulation parameters will be guided by previous reports of nVNS in patients. Patients will be trained on all appropriate methods for using the devices and asked to report the number of daily therapy sessions completed. Patients will be asked to continue their standard medication regimens which include in majority of cases 3 weekly IVIG (1 gm/kg) infusions, with or without steroids and plasma exchange.

- **Handheld dynamometer:** In the pediatric NM clinic we use a Jamar Handheld Dynamometer with reference range (in kilograms and pounds) for children ages 5-18 years. Both right and left hand grip strength would be measured. Best of the three attempts will be used in each hand. We routinely use dynamometer.
- **R-ODS:** Twenty four item motor scale based on day to day activities with a score of 0-48. The scale was designed for adult CIDP subjects however based on our experience in children the scale captures pediatric motor disability as well.
- **NCS metrics:** Motor nerve conduction studies are well tolerated in children. We routinely study median, ulnar, common fibular and tibial nerves on one side of the body. Distal and F wave latency, conduction velocity and amplitude will be recorded in all nerves. In addition, drop in motor amplitude and or temporal dispersion on proximal stimulation will be noted.

Specific Aim 2: Characterize serum cytokine profiles in CIDP patients receiving standard of care treatment and daily nVNS.

- Stimulation of the vagus nerve has been shown to reduce pro-inflammatory cytokine levels in both animal and human investigations just after one session. In addition to evaluating functional changes in CIDP patients, we will quantify pro-inflammatory cytokine levels known to be elevated in CIDP patients. Serum cytokine assay available at Children's Healthcare of Atlanta laboratory will be used (https://www.testmenu.com/choa/Tests/671572). The assay contains 13 cytokines (interleukin 2, 4, 5, 6, 8, 10, 12, 13, 17, interleukin 1 beta, tumor necrosis factor alpha, interferon gamma, interleukin 2 receptor (SD25) soluble). Available normative laboratory values for above-mentioned cytokines will be compared with the CIDP subject values. Blood samples will be collected at baseline and each subsequent follow up visit as shown in Table 1 for profiling of serum cytokine levels. By correlating physiological (changes in cytokine levels) and functional effects (NCS, R-ODS, grip strength), we will develop a mechanistic basis for how and why nVNS benefits pediatric CIDP patients.

III. Risks

Pediatric CIDP is a rare condition and disease course if often prolonged with relapse and remissions. The subject sample size is small and meaningful clinical/biochemical changes following an intervention in CIDP patient population takes months to years. In general, these limitations are true for the majority of rare pediatric neuromuscular conditions. Alternative approaches include comparing the study population with historical controls however well-done natural history studies in pediatric CIDP are missing. We also anticipate patient compliance challenges. The usage monitor on the nVNS device will allow us to account for that in the data analysis.

nVNS at the level of the neck in children has been used in multiple studies. Patients may experience irritation at the site of stimulation; however this typically subsides within 10-15 minutes post-stimulation. In addition, patients may experience soreness in the neck due to activation of muscles, which is expected to be temporary.

Rarely, EKG changes have been described with nVNS. The study design includes regular EKG checks and if any changes or abnormalities are noted, this will be deemed as serious adverse event (SAE) and lead to termination of device use in the study participants. A follow-up visit and EKG will be performed for these subjects and if EKG abnormalities persist, pediatric Cardiology evaluation will be requested.

IV. Potential Benefits

Reduction of systemic inflammation in CIDP patients will halt degradation of motor nerve conductions and improve functional outcomes such as hand grip strength/ disability scores. Furthermore, nVNS therapy may lead to significant cost reductions in treatment and life-long healthcare costs of CIDP patients. Benefits of nVNS to patients will also reduce the disease burden on the patient's family by easing the treatment process.

V. Inclusion and Exclusion Criteria

Inclusion criteria:

1. Diagnosis of CIDP based upon clinical/electrophysiological criteria
2. Patient should be on treatment for CIDP including IVIG and/ or steroids/ plasma exchange
3. 5-21 years of age

Exclusion criteria

1. Patients will be excluded from the study if they have inherited polyneuropathy, such as Charcot Tooth Marie disease.
2. Abnormal baseline EKG, heart disease, epilepsy, pregnancy, multiple sclerosis and diabetes mellitus.

VI. Informed Consent Process

All pediatric CIDP patients followed in neuromuscular clinic would be eligible for the study. Study coordinator or PI will approach and consent these patients and their parents. For subjects older than 6 years of age, assent will also be documented.

VII. Data Safety

Oversight of the progress and safety of the trial will be provided by the PI. Dr. Verma will act as the study monitor and will check the progress of study and patient safety at regular basis. He will be notified directly within 24 hours of any adverse event. He will also be checking the data collected every 8 weeks in order to stay on top of the data safety.

Adverse events are not anticipated, but any occurring will be documented and reported according to Emory IRB policies and procedures. Cumulative adverse events and study progress summary will be communicated to the IRB at the time of continuing review.

The PI will identify serious adverse events (SAE).

Serious adverse events will be reported to the Emory IRB within 48 hours by the PI via a written and email correspondence. A log of adverse events will be kept while the study is in progress and reported to Emory IRB study safety officer on quarterly basis.

All patient data will be kept on an encrypted hard drive with access only to the members listed in this application. Data will be de-identified by referring to patients through assigned ID numbers (CIDP#), data will be kept for the duration of the study until publications are complete. Once complete, data will be permanently destroyed by mechanically destroying the data storage devices and shredding any potential paper-based forms/data.

The principal investigator (PI) will perform and supervise all evaluations during the study period.

Trained personal (M.D.'s) will be present during the conduct of this study. In case of serious adverse event the subject will personally evaluated by the PI within 24 hours of occurrence. Adverse events and unanticipated events will be evaluated within five days of occurrence.

All data obtained during the study will be kept confidential with the study coordinator, and PI on the password protected Children's Healthcare of Atlanta (CHOA) network and research office at Scottish Rite Hospital

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