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1. Protocol title: Peripheral nerve ultrasound for diagnosis and prognosis of Guillain-Barré Syndrome: A pilot study

2. Purpose of the study:

The primary objective of the study is to determine if peripheral nerve ultrasound can be used as a supplemental tool to diagnose Guillain-Barré syndrome (GBS) in the acute setting and aid in prognosis. We hypothesize that ultrasound of the peripheral nerves of patients with GBS will show enlargement at the most proximal and distal segments, resulting in increased nerve size variability.

3. Background and Significance:

Guillain-Barré syndrome (GBS) is an immune-mediated, acute to subacute onset polyradiculoneuropathy that typically presents with symmetric, ascending weakness over the course of a few days, with approximately 30% of patients requiring supportive ventilation.[1] It is a monophasic disease with nadir reached by 4 weeks. In the acute setting, diagnosis is made by clinical history, physical examination, and presence of cyto-albuminological dissociation in the cerebrospinal fluid (CSF). However, CSF can be normal in up to one third of patients and is more likely to be normal early in the course.[2] Nerve conduction studies (NCS) are most helpful in confirming the diagnosis and defining subtypes. However, within the first few days, NCS are typically normal or may show only subtle signs such as prolonged F wave latencies. Given the high morbidity and mortality associated with GBS and evidence supporting benefit with the use of intravenous immunoglobulin (IVIG) or plasmapheresis (PLEX), treatment should be initiated as soon as possible.

Peripheral nerve ultrasound may be a noninvasive, inexpensive adjunct to aid in the diagnosis of GBS patients in the acute setting, particularly when lumbar puncture or nerve conduction studies cannot be performed.

Prior studies with ultrasound have found varying and relatively low percentages of patient with GBS that had significantly enlarged peripheral nerves, varying from 0% to 53% .[3,4,5] However, these studies included subjects with duration of symptoms ranging from weeks to years. Additionally, some studies performed in Asia cannot be generalized to North American populations given the relatively high percentage of acute motor axonal neuropathy (AMAN) variants in that region,[6,7] whereas AIDP is the most common variant in the United States.[1]

Interestingly, Grimm et al. 2015 found that enlargement of the vagus and cervical roots 5 and 6 without or with only slight enlargement of the other peripheral nerves had a high prediction for GBS. However, this study was again limited by a large range of time after onset (0.1 to 3 months).[8]Grimm et al. also compared GBS patients within 1-3 days of symptom onset to normal controls.[9] Cross-sectional area (CSA) of multiple sites of the median, ulnar and tibial nerves as well as the fibular, sural, vagal, and C6 nerves were measured. Enlargement of cross sectional area (CSA) in GBS patients compared to controls was statistically significant at all nerve sites except the proximal ulnar nerve, sural nerve, and C6 nerve root. However, there was quite a large range of overlap among the two groups with many GBS patient

values falling within the normal range. These studies were considered in designing the methods for this prospective study.

In the proposed study, we will image median, ulnar, cervical, and vagus nerve ultrasound in GBS patients within two weeks of symptom onset. We will compare these findings to other diagnostic and clinical measures including NCS measurements, CSF protein, respiratory status and ambulation on discharge. Additionally, we will compare intranerve CSA variability in these subjects compared to controls, which to our knowledge, has not been done before in GBS patients.

4. Design and procedures:

DATA COLLECTION

Part A: Investigational measures

All patients seen by the Duke Hospital inpatient neurology ward or consult services with suspected GBS (acute, progressive weakness with no alternative diagnosis) with onset of symptoms less than 30 days prior will be eligible for the study. Neurology housestaff will be asked to screen potential subjects. An equivalent number of age and gender matched controls will be recruited within the same time frame, for a total of about 50 patients. The patient controls will be recruited from hospitalized patients on the inpatient neurology service who are being treated for non-peripheral nerve disorders (e.g. epilepsy, multiple sclerosis, or stroke).

All patients will be 18+ years of age.

Patients with any history of multifocal motor neuropathy (MMN), prior Guillain-Barre syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), or hereditary neuropathy (e.g. Charcot-Marie-Tooth) will be excluded from both the GBS and control groups.

A Duke Electromyography Laboratory physician or technician blinded to the EMG/NCS results will perform an ultrasound of the bilateral ulnar nerves, median nerves, vagus nerves, and C6 and C7 nerve roots on Days 0 and 7 of admission. The nerves will be imaged in the axial plane. For the median nerve, CSAwill be recorded at the distal wrist crease, mid-forearm, cubital fossa, mid-humerus and axilla. For the ulnar nerve, CSA will be recorded at the distal wrist crease, forearm, mid-ulnar groove, mid-humerus, and axilla. In addition to these measures, the largest cross sectional area for the ulnar and median nerves will be recorded if present outside these defined locations. For the vagus nerve, the CSA will be measured at a single point in the axial plan at the level of the thyroid cartilage. For the cervical roots, CSA will be measured at a single point in the axial plane at the intrascalene level.

CSA will be measured using the continuous trace method, measuring the circumference. The ultrasound system used is an Esaote Biosound MyLab 70 equipped with an 18 MHZ linear array transducer.

Hypervascularity will also be assessed at the site of maximal enlargement of median and ulnar nerves. Hypervascularity is defined by Doppler ultrasound showing blood flow within the epineurium of median or ulnar nerve at sites of maximal enlargement. Vascularity will be rated on the following scale: 0=no blood flow seen, 1= rare pulsations, 2= scattered pulsations, not sustained, 3=sustained pulsations. Vascularity of the cervical nerve roots and vagus nerve will not be assessed given the proximity to multiple cervical vessels, which may confound interpretation.

Sum Medical Research Council (MRC) scales and hand grip measurements with a dynamometer will be obtained by physical examination at Days 0 and Day 7.

For relevant study procedures, if the patient is scheduled to be discharged prior to Day 7, the procedures scheduled for Day 7 will be performed prior to discharge as long as they occur on or after Day 4.

Subjects with GBS will be asked to describe their ambulatory function by telephone at 3 and 6 months after enrollment.

Part B: Data collected from standard diagnostic and therapeutic interventions

The medical records of enrolled patients will be monitored during admission for data required to enroll and for collection of history and data during admission (age, gender, chief complaint, duration of symptoms, alternative diagnoses explored, history of a prior diarrheal illness, NCS/EMG results, CSF cell count and protein, treatments administered, respiratory parameters (negative inspiratory force [NIF] and vital capacity [VC]), intubation duration, tracheostomy status, ambulatory status on discharge, and discharge location). Please see the attached case report form for complete details.

DATA ANALYSIS

Mean CSA of the median and ulnar nerves will be calculated, along with range, standard deviation and 95% confidence intervals. Following this, intranerve variability ratios will be calculated in patients and controls.

Intranerve cross-sectional area (CSA) variability for each nerve will be calculated as: maximal CSA/minimal CSA. Internerve CSA variability for each patient will be calculated as: maximal intranerve CSA variability/minimal intranerve CSA variability (Padua 2012).

The primary outcome will be to perform a statistical analysis using ROC curve to determine the sensitivity and specificity of different ultrasound measures and that will help determine which variable or combination of variables is best to use in determining whether the patient has GBS.

Secondary outcomes evaluated will include length of hospital stay, ambulatory status on discharge, respiratory function, strength, autonomic dysfunction, and GBS disability score.

5. Selection of subjects:

All patients seen by the Duke Hospital inpatient neurology ward or consult services with suspected GBS (acute, progressive weakness with no alternative diagnosis) with onset of symptoms less than 30 days prior will be eligible for the study. Neurology housestaff will be asked to screen potential subjects. An equivalent number of age and gender matched controls will be recruited within the same time frame, for a total of about 50 patients. The patient controls will be recruited from hospitalized patients on the inpatient neurology service who are being treated for non-peripheral nerve disorders (e.g. epilepsy, multiple sclerosis, or stroke).

All patients will be 18+ years of age.

Prisoners and employees will not be asked to participate, as these are potentially vulnerable populations.

6. Subject recruitment and compensation:

Patients will be asked to participate in the study upon admission. No financial compensation will be provided as patients will not incur any extra travel or significant loss of time in participating in the study.

7. Consent process:

Patients will be consented prior to ultrasound being performed. Patients who are unable to be consented due to transiently impaired cognition (such as during sedation or sepsis) will not be enrolled unless a healthcare power of attorney is available to provide consent. Once cognition is intact, the patients will be re-consented to determine if they will remain in the study.

8. Subject's capacity to give legally effective consent:

Patients unable to make their own medical decisions, except when caused by acute illness of sedation (see section 7), will not be asked to participate in the study.

9. Study interventions:

Study interventions, as described in section 4, are upper extremity nerve ultrasound, manual testing of muscle strength, and hand grip dynamometry.

10. Risk/Benefit Assessment:

Ultrasound of the extremities has been established as a safe procedure. No vulnerable populations (including prisoners, minors, or cognitively impaired adults) will be assessed.

Potential risks of the procedure are limited. No discomfort during examination is expected.

Standard infection control procedures will be utilized. Procedures will include cleaning the ultrasound probe between patients with an alcohol based solution. Persons with broken skin in the area designated for imaging will be excluded from the study.

A patient's decision to decline participation will not affect treatment in any way. It is unlikely that the individual patient will receive immediate benefit from participation. If any unexpected abnormalities are identified on US examination, the patient referring physician will be notified.

11. Costs to the subject:

Subjects will not incur additional costs from participation in this study.

12. Data Analysis & Statistical considerations:

At the completion of the study, the sensitivity and specificity of ultrasonographic parameters for the diagnosis of GBS will be determined using a ROC curve.

Ultrasound data will be correlated with disease severity and patient outcome (duration of hospitalization, respiratory measures, GBS disability score, modifed Erasmus GBS outcome score, NCS

measurements, ambulatory status on discharge, strength) as well as diagnostic certainty (Brighton score).

13. Data & Safety monitoring:

Data for this study will be analyzed at the completion of study enrollment. Safety monitoring will not be necessary as there are no risks to patient's health.

14. Privacy, data storage &confidentiality:

Please refer to section of the electronic application for full details. The database files will be kept on a secure computer network that can only be accessed by the investigators (Lisa D. Hobson-Webb and Natalia Gonzalez). All patient data in this project-specific database will be identified by a unique code number that cannot be related to individual patients. The key to this number will be kept secure in the principal investigator's locked office.

References:

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the peripheral nerves. Clin Neurophysiol. 2015 Nov;126(11):2216-25.

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