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**4. TITLE AND SUBTITLE**

Undiagnosed Small Fiber Polyneuropathy: Is It a Component of Gulf War Illness?"

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**14. ABSTRACT**

The term small-fiber polyneuropathy (SFPN) refers to body-wide dysfunction and degeneration of small-diameter axons that transmit pain and control the body’s autonomic functions. The vague, widespread symptoms of SFPN overlap substantially with those of Gulf War Illness (GWI). We propose that there may be a SFPN component to GWI. To identify and apply the best tests to diagnose SFPN in Gulf War-ill veterans, we are recruiting, screening, and testing normal control subjects and patients with definite SFPN to compare the sensitivity and specificity of the best current and potential new tests. We will then apply and compare results the best tests in Gulf War veterans with and without GWI to identify how often this diagnosable and treatable neurological illness is masquerading as GWI. By doing so, we will not only establish the relationship between GWI and SFPN, but will also determine which tests are the most diagnostically useful. This report summarizes progress against Specific Aim I of the basic statement of work.

**15. SUBJECT TERMS**

Gulf War Illness, Small-fiber polyneuropathy, SFPN, neurite, skin biopsy, autonomic function test, AFT, axon flare
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INTRODUCTION:

The term small-fiber polyneuropathy (SFPN) refers to body-wide dysfunction and degeneration of the small-diameter axons that transmit pain and control the body’s autonomic (involuntary) functions. The vague, widespread symptoms of SFPN overlap substantially with those of Gulf War Illness (GWI). SFPN is hard to diagnose clinically and requires special tests. We propose that there may be a SFPN component to Gulf War Illness. To identify and apply the best tests to diagnose SFPN in Gulf War-ill veterans, we are recruiting, screening, and testing normal control subjects and patients with definite SFPN to compare the sensitivity and specificity of the best current tests (skin biopsy and comprehensive autonomic-function testing (AFT)), as well as a potential new test (axon flare reflexes to vasodilators) (Aim I). We will then apply the best of these tests and compare results in Gulf War veterans with and without Gulf War illness to identify how often this diagnosable and treatable neurological illness is masquerading as Gulf War Illness (Aim II). By doing so, we will not only establish the relationship between Gulf War Illness and SFPN, but will also determine which tests are the most diagnostically useful and should be adapted for more widespread clinical use. This report summarizes progress against Tasks 1 and 2 of Specific Aim I of the basic statement of work which is included at Appendix 1.

PROGRESS AGAINST SPECIFIC AIMS:

The initial phase of this study is aimed at establishing normative neurite densities from a diverse normal population and identifying the test(s) of greatest utility in diagnosing small-fiber polyneuropathy, which has been identified as a strong need in the neurology community [1]. At this point the study is on track to collect data from the requisite number of subjects to make these determinations during Year 2. Progress against the sub-tasks scheduled to be accomplished or begun in the first year of this study (a, b, and c of Tasks 1 and 2 of Specific Aim I) is detailed below. Please refer to the Statement of Work, included at Appendix 1, for the complete study plan.

Specific Aim I. To determine which specific measurements of skin innervation, autonomic function, and skin blood flow provide the most sensitive, specific, and practical objective test for SFPN.

Task 1. Establish demographically correct skin biopsy norms. A cohort of 120 normal controls will be established to provide the necessary range of ages, sexes and ethnicities

a. Recruit, screen and test 120 normal controls. Some subjects have already been studied to provide preliminary data for this application. (months 1 – 6)

b. Multivariate data analysis to determine which of the three demographic variables tested (age, sex, race/ethnicity) influences the normal values for density of skin innervation and to generate the norms and limits between the normal and abnormal ranges necessary for clinical diagnostic use. (months 6 – 8)
c. To prepare and publish a manuscript in a high-impact neurological journal that will make these norms available for medical use worldwide. An internet version will also be made available. (months 8 – 20)

Task 1 centers on the establishment of demographically correct skin biopsy norms. Early work in skin neurite quantification by skin biopsy [2] has long-influenced later diagnostic efforts by skin biopsy by defining an abnormal neurite density with a single cutoff value regardless of age, gender, or ethnicity. More recent work has begun to show evidence of differences in neurite density by age and gender [3], but these studies, including a world-wide collaboration of neurite density databases [4] were either not ethnically diverse or did not identify ethnic differences in neurite density.

Task 1a: Our study seeks to expand on these findings by studying a cohort of 120 normal control subjects of various ages, genders, and ethnicities.

Methods: We have been recruiting subjects primarily through in-house advertisement and through the Research Study Volunteer Program (RSVP for Health) administered by our Clinical Research Program. All normal subjects are initially telephone-screened to rule out confounding health issues. In addition, normal subjects first undergo a 2-hour fasting glucose-tolerance test (GTT) to rule out diabetic neuropathy.

Skin biopsies are performed in our JCAHO-accredited laboratory. After informed consent, a site (10 cm above the ankle) is anesthetized and one or two 2- or 3mm diameter skin punches are removed using sterile technique and the site covered with a Band-Aid. Samples are immediately fixed and then sectioned (using a freezing sliding microtome) and processed using standard methods. For PGP9.5-IR, Zamboni’s fixative, 50 micron sections, and a 1:1200 dilution of polyclonal antibody specific for the pan-axonal enzyme ubiquitin hydrolase (PGP9.5) are used, followed by standard DAB labeling. For each biopsy, a single morphometrist then counts the total number of separate immuno-positive neurites within the entire epidermis which is then normalized to the skin surface area to yield a neurite density per square millimeter of skin surface.

Outcomes: We have already studied the 120 normal controls for Task 1a but will ultimately exceed that because (1) we are able to pool results of prior studies in our laboratory (using identical techniques) with those obtained under this study and (2) we also find that we are recruiting additional controls because we need additional subjects who can undergo the complete set of tests (glucose tolerance test, AFT, skin biopsy, axon flare) and many of the subjects who were studied previously are no longer available to be studied further (see Task 2, below). Although we continued to study additional normals throughout the year, our total for Task 1a remains 187 subjects, the same total as of the third quarter of Year 1. This is because we removed 14 subjects from the analysis either for pre-existing conditions that were not disclosed during the initial screening, or once it was demonstrated by 2-hour fasting glucose tolerance test that they had impaired glucose tolerance (pre-diabetes), as defined by criteria of the American Diabetes Association.

<table>
<thead>
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<td>80-89</td>
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<td>Total</td>
<td>187</td>
</tr>
</tbody>
</table>

Table 1. Distribution of normal subject ages
Association. The age distribution of the included subjects is summarized in Table 1. Of the subjects listed in Table 1, four were recently studied and are still awaiting analysis of their biopsies.

**Task 1b:** In addition to the adult normal controls listed in Table 1, we have also biopsied 25 youngsters aged 14-17 through other studies. Although they are not part of this study, their biopsy results anchor the lower end of the normal biopsy curve from which the multivariate analysis is derived. Thus, their biopsies will remain part of the data set for the analysis of this study even though they were not studied under this grant. A logarithmic scale provided the best linear regression fit to the full data set ($R = 0.65$) and is presented in Figure 1.

![Figure 1. Logarithmic fit to neurite densities of 208 normal controls. Subjects under age 18 (not part of this study) are in red](image)

We met with a statistician to refine the multivariate analysis of the normal subject biopsies. We developed a multivariate regression that includes age, gender, and ethnicity. So far, the study is insufficiently powered in Black, Hispanic/Latino, or Hawaiian/Pacific Islanders to be significant, but we do have sufficient Asians for significance. The differences between the Asian and non-Asian populations in this cohort (youngsters and adults) is illustrated in Figure 2, with complete ethnic and gender details of the cohort provided in Table 2.
We compared neurite densities among Asian and non-Asian populations of the same age range. The results are summarized in Table 3, and indicate that there is a significant difference in neurite density between Asians and non-Asians (p=0.046) while the age distribution among the two groups was not significantly different (p=0.57).
We also compared neurite densities among females and males of all ethnicities over the entire range of ages. The results are summarized in Table 4 and indicate that there is a significant difference in neurite densities between females and males ($p = 0.006$), while the age distribution among the two groups was not significantly different ($p=0.46$).

Thus a multivariate regression analysis that accounts for the variations attributed to age, gender, and ethnicity is appropriate and is presented in a draft Equation (1). Since we are still recruiting normal controls to fill out the populations needed for Tasks 2a and 2c of Specific Aim I, the
current regression analysis should be considered preliminary and will be modified as the final number of controls is tested. As we are nearing the completion of this phase of the study (Task 1a, 1b) a manuscript is being prepared for publication of these results (Task 1c).

**Equation (1):**

\[
\text{Log (neurite density)} = 2.6627 + 0.0958(\text{gender}) - 0.0066(\text{age}) + 0.0678A - 0.0439B + 0.0063L - 0.0110H
\]

Where
- neurite density is in neurites/mm²
- gender = 1 if female, 0 if male,
- age is in years,
- A = 1 if Asian, otherwise = 0,
- B = 1 if Black, otherwise = 0
- L = 1 if Hispanic/Latino, otherwise = 0
- H = 1 if Hawaiian/Pacific Islander, otherwise = 0

**Task 2. Compare the diagnostic sensitivity and specificity of skin biopsy, AFT, and axon-flare measurements to establish best tests for SFPN.** Data will be collected from cohorts of 40 screened normal volunteers, SFPN patients, and symptom-matched control patients with severe osteoarthritis.

a. Recruit 40 normal subjects from among the 120 being studied by skin biopsy for Aim I for additional study with AFT and axon-flare measurements. (months 3 – 12)

b. Recruit 40 subjects with definite SFPN from among the several hundred already evaluated for clinical care at Mass. General Hospital by skin biopsy and AFT for additional study of axon-flare measurements. (months 8 – 18)

c. Recruit 40 severe osteoarthritis of the hip or knee from among the thousands such patients followed at Mass. General Hospital for study by skin biopsy, AFT, and axon-flare measurements. (months 8 – 18)

Task 2 will provide the data to establish the best test for SFPN. We are comparing the results of 3 diagnostic tests for SFPN (skin biopsy, AFT, and axon flare) to identify which has the best predictive value. In addition, we are ruling out other potential sources of SFPN through questionnaire and 2-hour fasting glucose tolerance test (GTT). We are studying osteoarthritis subjects as a positive control to demonstrate that although the osteoarthritis subjects are also experiencing chronic pain, as do the SFPN patients, their pain has a non-neuropathic origin, and thus peripheral nerve test results from the osteoarthritis subjects should not differ significantly from the normal controls.

**Methods:** We have been recruiting subjects through in-house advertisement and through the Research Study Volunteer Program (RSVP for Health) administered by our Clinical Research Program. To the extent possible for normal controls, we have been inviting previously studied
subjects to continue in this study. Small-fiber polyneuropathy (SFPN) subjects from the neurology practice at Massachusetts General Hospital are also invited to participate if they have received a definite diagnosis of SFPN from a neurologist.

Autonomic Function Testing (AFT) consists of four specific separate tests that are routinely used and endorsed for clinical diagnostic testing for small-fiber polyneuropathy. We now have AFT equipment in our laboratory, and the tests are administered by personnel trained by the manufacturer (WR Medical Electronics, Stillwater, MN). The specific tests are (1) QSART (quantitative sudomotor axon reflex test) where sweat production is quantitated from the standard forearm, proximal leg, distal leg, and foot sites in response to iontophoresis of acetylcholine; (2) heart rate response to deep breathing where heart rate variability during inspiration and expiration is measured for at least 5 cycles; (3) beat-to-beat heart rate and blood pressure responses in phases II and IV of the Valsalva maneuver where heart rate variability is measured while the subject is asked to blow into a bugle to maintain a column of mercury between 40 and 50 mm; and (4) beat-to-beat heart rate and blood pressure responses to tilt where continuous blood pressure and heart rate monitoring is performed for 5 minutes with the subject supine, then the subject is placed in an 80 degrees heads-up tilt position for 10 minutes and subsequently returned to supine for an additional 5 minutes of recording.

Laser Doppler measurements of skin blood-flow and axon flare are performed in our laboratory using equipment from Moor Instruments Ltd, Devon, UK. Changes in blood flow rate are measured in response to a vasodilator (histamine or acetylcholine) which is introduced into the skin via iontophoresis. A hollow plastic ring is affixed to a subject’s skin which positions two fiber-optic laser leads, and is also a reservoir for the vasodilator. After measuring baseline blood flow, a current is applied to the liquid reservoir in the ring to drive the charged vasodilator molecules into the skin. Axon flare intensity measurements are taken continuously over time while a laser-Doppler imager provides a sequence of blood flow (flux) maps, taken at predetermined intervals.

**Outcomes:** We accelerated our progress against Task 2 by acquiring our own Autonomic Function Test (AFT) equipment. Prior to that we relied on the limited availability of a clinical AFT apparatus for our studies. We already possessed axon flare equipment prior to this study. Our progress against Task 2 is summarized below.

Tasks 2a, 2b, and 2c: Table 5 summarizes the progress of normal, osteoarthritis, and SFPN subject recruitment under Task 2. 28 normal control subjects have undergone the full range of tests and 9 others are in various stages of completion. 5 other normal controls have been screened and are ready for study. 11 osteoarthritis controls have undergone the full range of tests and 3 others have been screened and are ready for study. One difficulty in recruiting osteoarthritis controls is that, as a condition mostly

<table>
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<th>GTT</th>
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<td>No. of Normal Control Subjects (target 40)</td>
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<tr>
<td>No. of SFPN subjects (target 40)</td>
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of the elderly and/or overweight, there is a greater prevalence of impaired glucose tolerance (IGT). We rejected 4 osteoarthritis subjects from the study for having IGT. All 40 SFPN subjects have been studied with the full range of tests.

**KEY RESEARCH ACCOMPLISHMENTS:**

- Young subjects (below age 22) show a “superabundance” of skin neurites. Although teenagers (below age 18) are not part of this study, their neurite densities confirm the findings in the young adult subjects, and also anchor the lower end of the neurite density curve, thus providing a more accurate normative fit.
- Among normal controls, Asian subjects show a significantly higher neurite density in the skin than non-Asian subjects
- Among normal controls, female subjects show a statistically significant higher neurite density in the skin than male subjects
- There is insufficient power in the number of subjects in other ethnic groups to define significant differences in neurite densities
- A logarithmic scale provided the best regression fit to the experimental skin biopsy data.
- A preliminary multivariate representation of normative skin biopsy data was developed which, once finalized, will be of great medical importance in defining non-normal neurite densities for diagnostic purposes.

**REPORTABLE OUTCOMES:**

While this study is still in an early stage, work that culminated in several abstracts prior to this study is being carried over into this work to add significance to the findings. For instance, we presented preliminary results that indicated a superabundance of skin neurites in youngsters and a dependence of skin neurite density on age, gender, and ethnicity [5]. We also retrospectively and prospectively explored which diagnostic tests may have better predictive value for small fiber polyneuropathy among a small initial cohort of SFPN patients and normal controls [6].

**CONCLUSION:**

In its first year, this study has demonstrated progress toward its first significant outcome, namely a new set of normative neurite densities obtained from skin biopsy. Through multivariate analysis, these values provide a more accurate means of diagnosing small fiber polyneuropathy using skin biopsy, taking into account the influence of age, gender, and ethnicity. Recruitment of subjects to accomplish the remaining goals of this study is in progress and is proceeding according to schedule. In Year 2, the multivariate normative neurite density analysis will be complete and an additional analysis to establish the best test(s) for SFPN diagnosis will be accomplished. The results of these analyses will then be applied to the specific study of Gulf War veterans, which will begin in Year 2 and continue into Year 3.
REFERENCES:


Appendix 1

Statement of Work under W81XWH-10-1-0534

The timeline at page 3 of the Statement of Work has been updated to show progress of the individual subtasks. Green triangles indicate completed tasks, yellow is tasks in progress, and gray includes those tasks beyond Year 1.
Undiagnosed small-fiber polyneuropathy - Is it a component of Gulf-War Illness?

**Background:** The term small-fiber polyneuropathy (SFPN) refers to body-wide dysfunction and degeneration of the small-diameter axons that transmit pain and control the body’s autonomic (involuntary) functions. SFPN typically causes chronic pain, gastrointestinal symptoms, fatigue, dizziness, chronic headache, and skin abnormalities - complaints that overlap substantially with Gulf War Illness (GWI). Because SFPN produces vague, widespread symptoms, it is hard to diagnose clinically and requires special tests. In Aim I we will recruit, screen, and test normal control subjects and patients with definite SFPN from among the hundreds seen at Mass. General to compare the sensitivity and specificity of the best current tests (skin biopsy and comprehensive autonomic-function testing (AFT)), as well as a potential new test (axon flare reflexes to vasodilators). In Aim II, we will apply the best of these tests and compare results in Gulf War veterans with and without Gulf War Illness to identify how often this diagnosable and treatable neurological illness is masquerading as GWI. By doing so, we will not only establish the relationship between Gulf War Illness and SFPN, but will also determine which tests are the most diagnostically useful and should be re-engineered for more widespread clinical use. Most procedures in this study, including access to patient records, telephone screening, and skin biopsy and axon flare testing are already approved by the Partners Human Research Committee’s Institutional Review Board (IRB) under protocol #1999-P-009042, “Laboratory Evaluation of Neuropathic Pain”.

**Specific Aim I.** To determine which specific measurements of skin innervation, autonomic function, and skin blood flow provide the most sensitive, specific, and practical objective test for SFPN.

**Task 1. Establish demographically correct skin biopsy norms.** A cohort of 120 normal controls will be established to provide the necessary range of ages, sexes and ethnicities

a. Recruit, screen and test 120 normal controls. Some subjects have already been studied to provide preliminary data for this application. (months 1 – 6)

b. Multivariate data analysis to determine which of the three demographic variables tested (age, sex, race/ethnicity) influences the normal values for density of skin innervation and to generate the norms and limits between the normal and abnormal ranges necessary for clinical diagnostic use. (months 6 – 8)

c. To prepare and publish a manuscript in a high-impact neurological journal that will make these norms available for medical use world-side. An internet version will also be made available. (months 8 – 20)

**Task 2. Compare the diagnostic sensitivity and specificity of skin biopsy, AFT, and axon-flare measurements to establish best tests for SFPN.** Data will be collected from cohorts of 40 screened normal volunteers, SFPN patients, and symptom-matched control patients with severe osteoarthritis.

a. Recruit 40 normal subjects from among the 120 being studied by skin biopsy for Aim I for additional study with AFT and axon-flare measurements. (months 3 – 12)

b. Recruit 40 subjects with definite SFPN from among the several hundred already evaluated for clinical care at Mass. General Hospital by skin biopsy and AFT for additional study of axon-flare measurements. (months 8 – 18)

c. Recruit 40 severe osteoarthritis of the hip or knee from among the thousands such patients followed at Mass. General Hospital for study by skin biopsy, AFT, and axon-flare measurements. (months 8 – 18)
Specific Aim II. To use the best of these tests to determine the prevalence of SFPN among GW-ill veterans recruited with the assistance of the VA Decision Support System, and to compare SFPN prevalence to the prevalence in unaffected Gulf-War veterans and our demographically matched civilian controls.

Task 3: Determine prevalence of SFPN in Gulf War-ill veterans. The best tests identified above will be administered to groups of normal Gulf War veterans and veterans suffering from Gulf War Illness.

a. Recruit healthy and ill Gulf War veterans. Cohorts of 150 of each veteran group will be recruited by a combination of electronic medical-record searches at Mass. General Hospital, VA databases, and DoD databases. Additional IRB approvals external to MGH may be required. (months 18 – 30)

b. Test veteran cohorts with best test(s) of Task 3 to determine prevalence of SFPN among Gulf War Ill veterans. (months 22 – 30)

c. Data analysis to determine and compare the prevalence of SFPN in Gulf War ill and controls. Multivariate data analysis to determine which of the tests have greatest potential for clinical diagnostic use. Positive and negative predictive value, diagnostic sensitivity and specificity, invasiveness and cost will be considered. Tests that complement or overlap will be identified. (months 26 – 32)

d. To prepare and submit for publication a manuscript in a high-impact medical journal that will make these findings available world-side. (months 32 – 36)
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<td>Analysis to generate norms</td>
<td>Prepare and publish manuscript</td>
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<td>Recruit and test SFPN patients – axon flare</td>
<td>Recruit and test osteoarthritis patients – biopsy, AFT, axon flare</td>
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<td>Prepare and publish manuscript</td>
<td>Recruit Gulf War veterans</td>
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<td></td>
<td>Test veterans with best tests</td>
<td>Data analysis</td>
<td>Prepare and submit manuscript for publication</td>
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