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14. ABSTRACT
Damage to the small nerve fibers that sense pain and regulate function of internal organs results in small-fiber polyneuropathy (SFN). SFPN symptoms include unexplained chronic widespread pain (CWP) and chronic multisymptom illness (CMI) similar to Gulf War Illness. Our prior research demonstrated that SFPN is prevalent in such CWP and CMI syndromes and that it can have onset at a young age. Given these non-specific symptoms, objective testing is recommended for SFPN diagnosis. In the third year of this study Global experts participated in additional rounds of a Delphi process to determine the most reliable markers for SFPN (Case Definition). We also developed a comprehensive database of SFPN patients and well-characterized controls with which to validate the Case Definition. The diagnostic tests recommended under the Case Definition were applied to Veterans and age-matched controls to look for the prevalence of SFPN.

15. SUBJECT TERMS
Neuropathy, Gulf War Illness, chronic widespread pain, chronic multisymptom illness, small-fiber polyneuropathy, case definition

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1. INTRODUCTION:

Nerves contain motor, sensory, and autonomic axons, most of which are the small-diameter, unmyelinated C-fibers or thinly myelinated A-delta fibers that sense pain and regulate the function of internal organs and tissues. The farthest ends of these long axons easily malfunction and degenerate if their oxygen, nutrient, or energy supply is compromised, which results in small-fiber polyneuropathy (SFPN). SFPN symptoms include unexplained chronic widespread pain (CWP) and chronic multisymptom illness (CMI), including cardiovascular, gastrointestinal, microvascular, and/or disordered sweating, which contributes to heat and exercise intolerance and fatigue, similar to Gulf War Illness. Given these non-specific symptoms, objective testing is recommended for SFPN diagnosis. Our prior research suggests that SFPN is prevalent in CWP and CMI syndromes [1]. We additionally discovered SFPN that affects adolescents and adults [2]. This early-onset SFPN usually begins in adolescence or early adulthood but can linger to cause CWP and CMI for decades, like Gulf War Illness. Importantly, some causes of early-onset SFPN can be treated and even cured. Our previous preliminary data showed that among 38 Gulf War Veterans and 41 matched controls, 49% of veterans had objective evidence of SFPN vs. 12% of controls [3], a result that remains true among a more recent cohort of 49 Gulf War Veterans and 51 matched controls [4]. However, interpretation is uncertain as there remains no Case Definition of SFPN. We recruited a group of global experts and used validated methods via a secure website to achieve consensus on the elements of a Case Definition of SFPN. We brought these findings to a meeting of the ACTTION committee that met with the goal of developing a Case Definition for SFPN. To date, the ACTTION Case Definition is not finalized. However, we applied the draft Case Definition criteria to an extensive database of patients and well-characterized healthy controls that we recruited. We then applied the draft criteria in combination with clinical tests, including specific blood tests that we identified [5] to not only look for the prevalence of SFPN among Gulf War veterans, but also to look for potentially treatable causes, such as immune-mediated factors [6].

2. KEYWORDS:

Neuropathy, Gulf War Illness, chronic widespread pain, chronic multisymptom illness, small-fiber polyneuropathy, case definition

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Objective/Hypothesis:
To determine the prevalence and clinical significance of undiagnosed small-fiber polyneuropathy among Gulf War veterans, and to look for potentially treatable causes of SFPN associated with Gulf War Illness.

Specific Aims:

Aim I: To develop a working Case Definition of SFPN to help physicians confirm or refute clinically suspected cases and for research use, and then to objectively diagnose the presence or absence of SFPN among Gulf War veteran using validated anatomical and physiological diagnostic tests.

Aim II: To perform blood and skin-biopsy tests for the specific treatable causes of SFPN and to compare the prevalence of identified causes in Gulf War veterans with or without SFPN to evaluate the specificity of association.

Within these Specific Aims, three tasks were performed during this study. Please note that we obtained permission to extend the period of performance of this study for a fourth year at no cost, in order to continue recruiting study subjects to achieve the necessary significance in our results:

Task 1. Retrospective analysis and application of Delphi method to develop a Case Definition. A panel of Experts will contribute benchmark cases through which key health history parameters are used to build the Case Definition.

Task 2. Apply validated tests to veterans and diagnose SFPN (and controls in Aim II). Collect evidence pertaining to SFPN from a cohort of 80 veterans and, according to the new Case Definition, screen them for the presence or absence of SFPN in order to establish causality.

Task 3: Identify treatable causes of SFPN in Gulf War veterans. Acquire data about the causality of SFPN through tests administered to all subjects to identify abnormal results indicative of SFPN.

What was accomplished under these goals?

Aim I:

We accomplished the following under Aim I (Task 1):

1. We obtained IRB and HRPO approval for the study, and amended the protocol to meet the requirements of both the MGH IRB and DOD HRPO.

2. We engaged the Informatics Team in the MGH Department of Neurology to create an Internet site to serve as the entry point to a secure platform where the Global Panel of Experts could upload responses to be used for the Delphi process of developing the Case Definition of SFPN. The public portion of the website may be accessed at http://NeuropathyCommons.org .

3. We continued to improve the Internet site that serves as a secure platform for the Delphi process. We expanded its content to be a source of pertinent information on SFPN for patients and researchers, and added a link to this study as a recruitment tool. We also improved functionality of the user-interface to better enable participation in the Delphi process by the Global experts.

4. We collected responses from the Global experts to two sets of questions, enabling us to narrow the criteria toward a Case Definition of SFPN by applying the Delphi process. The Delphi process is characterized by sets of questions posed to experts who are given an opportunity to modify their responses in successive rounds of responses until consensus is achieved [7] most often defined as percent agreement. The list of participating experts is in Appendix 1.

The first set of questions underwent two rounds of responses. The second set of questions underwent a first round of responses, and since most questions in that round already trended toward consensus, we did not require a second round of responses. The specific questions and results of each round are presented in Appendix 2.

We used these data to draft Case Definition criteria which, by consensus of our panel of experts, included **skin biopsy** and **composite autonomic Function testing (AFT)**. We used these as the basis for a published manuscript on the efficacy of Intravenous Immunoglobulin for treatment of apparently autoimmune small-fiber neuropathy, included as Appendix 3 [6] which validated our approach to apply them to this study.

5. We created an Access database as a source of clinical cases and research results with which to test the Case Definition. The database consists of patients with diagnoses of small-fiber neuropathy from the electronic medical records of Massachusetts General Hospital, and also healthy controls who have been studied in our laboratory with the same standard tests for neuropathy that we proposed as part of the Case Definition. The database currently contains data on 4,397 subjects consisting of 3,864 patients and 533 healthy controls. The prevalence of SFPN can be retrospectively identified while applying the Case Definition.

6. Additionally, Dr. Oaklander was invited to participate and contribute to a 2018 meeting on small-fiber neuropathy organized by the ACTTION/CONCEPPT organization. ACTTION (Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks) is a public-private partnership with the FDA. CONCEPPT (the Consortium on Clinical Endpoints for Peripheral Neuropathy Trials) is a subgroup of ACTTION. These meetings are attended by and contributed to by representatives from academia, FDA, NIH and industry and they are funded by the FDA, the NIH and specific pharmaceutical manufacturers. The primary goal of this specific meeting was to develop and publish the first consensus diagnostic criteria (inclusion and exclusion) recommended for clinical trials in small-fiber neuropathy and conforming to NIH and FDA standards. Coparticipants in the Dephi and ACTTION/CONCEPPT meeting were as follows

David Herrmann, MD (University of Rochester, Rochester, NY)
Ahmet Höke, MD, PhD (Johns Hopkins Hospital, Baltimore, MD)
Anne Louise Oaklander, MD, PhD (Massachusetts General Hospital, Boston, MA)
A. Gordon Smith, MD (University of Utah, Salt Lake City, UT)

Catharina Faber, MD, PhD (Maastricht University Medical Centre, Maastricht, Netherlands)
Giuseppe Lauria, MD (Instituto Carlo Besta, Milan, Italy)

Thus, these will supersede the proposed use of expert opinion to formulate diagnostic criteria. Dr. Oaklander brought our experience in collecting consensus opinion on a Case Definition to this meeting and will request to include this award in the ACTTION/CONCEPPT Acknowledgements. To date the meeting participants are still working on draft criteria for a formal Case Definition. Although not yet finalized, these will likely include the requirement for at least typical sensory symptom in an anatomically plausible location for at least 3 months, plus at least one sensory abnormality as assessed from physical examination, and abnormally reduced density of epidermal neurites on skin biopsy. The consensus case definition will confirm skin biopsy, performed, processed, and analyzed as we do, as the gold standard test for small-fiber neuropathy and thus necessary for Case Definition. As of now, the panel has not finalized recommendations regarding use of AFT.

We accomplished the following under Aim I (Task 2):

We continued to collect evidence of SFPN based on draft Case Definition criteria (skin biopsy, composite autonomic function test, as recommended by our Global Panel of Experts) from Gulf War Veterans and age-matched controls. We then aggregated those data with data collected from previous award GW093049.

Among Gulf War Veterans studied under this award (n=14)
6/14 (43%) have abnormal skin biopsy results (among which none had abnormal AFTs, one had borderline AFT)

Among healthy controls studied under this award (n=19)
3/18 (17%) for whom results are available have abnormal skin biopsy results
2/19 (11%) have abnormal AFT results
Note: 7/19 controls identified themselves as Veterans (not Gulf War) and 2/7 of them had abnormal skin biopsies

Total of Veterans and Controls studied in previous award GW093049 added to this study:
Among Gulf War Veterans (n=50):
40% (20/50) had abnormal skin biopsy results, 10% (5/50) had abnormal AFT

⇨ 48% (24/50) of Gulf War Veterans had either abnormal skin biopsy or AFT (1 had both abnormal biopsy and AFT)

Among healthy controls (n=60):
13% (8/60) had abnormal skin biopsy results, 5% (3/60) had abnormal AFT

⇨ 15% (9/60) of healthy controls had either abnormal skin biopsy or AFT (2 had both abnormal biopsy and AFT)

Aim II:

We accomplished the following under Aim II (Task 3):

1. We performed retrospective studies under Aim II to identify the blood tests that may have the best predictive value for SFPN:

We began by focusing on the diagnostic tools remaining to be developed under Specific Aim II to help identify SFPN, specifically blood tests for markers of SFPN. To gain perspective on the relative utility of the various tests, we retrospectively examined the prevalence of abnormal blood test results among SFPN patients to see if the tests had positive predictive value for SFPN, and also considered their cost-effectiveness in light of their predictive value. The goal was to evaluate the diagnostic utility of commonly available neuropathy-related blood tests in patients with idiopathic SFPN and formulate evidence-based recommendations for testing.

To do so, we surveyed the yield and cost of all 21 commonly available blood tests reported in the literature as useful for identifying causes of SFPN (Table 1) [8,9,10]. Results from within one year before or after the test for SFPN were included. With IRB permission, we examined the

records of a large cohort of patients with objectively confirmed predominantly idiopathic SFPN at MGH during calendar year 2013 and at least one blood-test result available. The objective tests were distal-leg skin biopsy, autonomic function testing (AFT) and surgical nerve biopsy [11].

We found that out of 195 qualifying patients 57% had more than one abnormal blood test result, and among those patients who had at least 10 of the recommended blood tests done, 91% had at least one abnormal result. The most prevalent blood-test abnormality was high angiotensin-converting enzyme (ACE), but as no patients had sarcoidosis diagnoses or diagnostic chest imaging we identified these results as entirely nonspecific in this context and recommended no longer routinely performing this test. All blood-test markers of diabetes and prediabetes were below population prevalences, indicting no specific association with SFN. In contrast, 44% had blood-test abnormalities consistent with dysimmunity (ESR, ANA, C3, C4), all higher than population prevalences, suggesting possible associations and supporting routine use of these tests in patients with SFN of uncertain cause.

We presented posters summarizing these preliminary results at the 2015 Meeting of the Peripheral Nerve Society (PNS) [12] and the 2015 Meeting of the American Neurological Association (ANA) [13] (Appendices 4 and 5). The final 2016 publication of these results is included as Appendix 6 [5]

Table 1. Tests and definition of abnormal

ACE (high)
2 hour GTT value 140-199 mg/dl *
Fasting glucose (100-126 mg/dl) *
ESR (high)
ANA (>1:160)
Triglycerides (high)
Hgb A1c (≥ 5.7%)
Hemoglobin (low)
C4 (low)
Liver AST/ALT (high)
C-reactive protein (high)
C3 (low)
AntiRo/SS-A, AntiLa/SS-B
Lyme
Hgb A1C (≥ 6.5%)
SPEP/IFIX
Celiac antibodies (IgA TTG) (high)
Creatinine (high)
Thyroid stimulating hormone (low)
Folate (low)
Vitamin B12 (low)
Hepatitis C antibodies
Fasting glucose (≥ 126 mg/dl) *
2 hour glucose (≥ 200 mg/dl) *
* note: all GTT and glucose measurements are considered one test

As a result, we narrowed the applicable blood tests for this study to those considered most predictive and most cost-effective (see Appendix 7).

2. We recruited Gulf War Veterans and age-matched controls for study with the specific tests identified as having the best predictive value for SFPN. We then applied the diagnostic tests with most utility to Gulf War Veterans who are additionally well-characterized by history, skin biopsy, and composite autonomic function testing; and to age-matched controls, to look for the prevalence of markers of SFPN that are indicative of causality. We compared blood test results from controls with those from Gulf War Veterans.

Among Gulf War Veterans studied under this award (n=14):
10/10 Veterans who completed the suite of blood tests show at least one abnormal result, but no pattern has emerged from the variety of abnormal results, some of which are slight abnormalities. 4 Veterans displayed abnormal ANA, and one displayed abnormal levels of complement C3, but only two of those Veterans had skin biopsies considered indicative of neuropathy.

Among healthy controls studied under this award (n=19):
17/17 for whom blood test results are available show at least one abnormal result
6 had abnormal ANA, but only one has a skin biopsy indicative of neuropathy.

Regarding inflammatory markers (ESR, C3, C4, ANA, SPEP, and tests for Celiac, Sjögren's, and monoclonal gammopathy) the only signals emerging more commonly were high ANA. However, high ANA was equally prevalent in Veterans as in controls (29% and 26%, respectively).

We also performed a brief neurological exam on each Veteran and matched control. We used the Mass General Neuropathy Exam Tool (MAGNET) which is an exam that incorporates the Utah Early Neuropathy Scale [14] and adds tests specifically validated for assessing small-fiber neuropathy.

Among 14 Gulf War Veterans, MAGNET scores averaged 4.21 (range 0-15, St Dev 4.41)
Among 19 Healthy Controls, MAGNET scores averaged 1.92 (range 0-5.5, St Dev 2.20)
P=0.058 (trend, but not statistically significant)

Total of Veterans and Controls studied in previous GW093049 added to this study:
Gulf War Veterans (n=50):
40% (20/50) had abnormal skin biopsy results, 10% (5/50) had abnormal AFT
48% (24/50) of Gulf War Veterans had either abnormal skin biopsy or AFT (1 had both abnormal biopsy and AFT)

Controls (n=60):
13% (8/60) had abnormal skin biopsy results, 5% (3/60) had abnormal AFT
15% (9/60) had either abnormal skin biopsy or AFT (2 had both abnormal biopsy and AFT)

What opportunities for training and professional development has the project provided?

Nothing to report. This project is not intended to provide training opportunities. Nonetheless, study staff do gain additional clinical and research skills through their participation.

How were the results disseminated to communities of interest?

This project has developed an Internet framework to increase awareness within the affected community and to promote participation in this research project. The website has pages specifically dedicated to patients and their issues, providing resources for information including our research efforts. As such, it will act as an outreach and recruiting tool for Gulf War Veterans among others affected by SFPN.

We presented preliminary results under Aim II at two scientific meetings (Peripheral Nerve Society and the American Neurological Association) as described above. We published the study of relevant blood tests under Aim II in the *Journal of Neurology* as described above.

We also participated in a meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses (the RAC) in April 2017 at which we presented results of our prior studies and progress

under our current studies to representatives of Veterans Affairs, researchers, Veterans, and the public.

We also presented an abstract of preliminary combined results of AFT and biopsy results of this study combined with prior award GW093049 at the 2018 Meeting of the International Association for the Study of Pain (IASP) [4].

What do you plan to do during the next reporting period to accomplish the goals?

Not applicable.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

A goal of this project was to generate a formal Case Definition for small-fiber polyneuropathy which is intended to guide future practice of diagnosticians. Toward that goal, we created a website with public and private Internet pages, to raise awareness of SFPN among Veterans, the general population, and health care professionals through the public pages, and to allow global experts to access the private (secure) pages to answer questions to validate the consensus Case Definition of SFPN. What we learned from the project's studies and from our expert consensus influenced the recommendations of the ACTTION/CONCEPPT panel that will publish the actual Case Definition.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

As described above, public awareness and attitudes toward SFPN and its sufferers should be impacted by this project.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

There have been no changes in our approach, nor are any changes anticipated.

Actual or anticipated problems or delays and actions or plans to resolve them

It took longer to develop the Case Definition as the responses from the Global experts in successive rounds of the Delphi process took longer than anticipated. We increased interaction with the Global experts to accelerate consensus on the key parameters of SFPN, and were able to approach consensus on the second set of questions. Although the expert opinions approached but did not definitively achieve consensus, the provisional acceptance of a manuscript which applied our draft Case Definition validated our approach and allowed us to proceed with recruitment of study subjects even though not all the tests were defined. To accommodate this

timeline, we obtained permission to extend the period of performance of this study. The plan to resolve this was to abrogate developing the first case definition to the ACTTION/CONCEPPT concept committee that Dr. Oaklander participated in and contributed insights gained from the Delphi process.

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals.

Not applicable.

Significant changes in use of biohazards and/or select agents

Not applicable.

6. PRODUCTS:

Publications, conference papers, and presentations.

Journal publications

Lang M, Treister R, Oaklander AL. Diagnostic value of blood tests for occult causes of initially idiopathic small-fiber polyneuropathy. *Journal of Neurology* 2016 Dec;263(12):2515-2527. Epub 2016 Oct 11.

Liu X, Treister R, Lang M, Oaklander AL. IVIg for apparently autoimmune small-fiber polyneuropathy: First analysis of efficacy and safety. *Therapeutic Advances in Neurological Disorders*, 2018 Jan 8;11:1756285617744484. PMID: 29403541.

Other publications, conference papers, and presentations.

Preliminary results of studies related to Aim II were presented in poster form at two scientific meetings:

Lang M, Treister R, Oaklander AL. Cost/Benefit Analysis of Blood Tests for Causes of "Idiopathic" Small-Fiber Polyneuropathy (SFPN). Presented to the Peripheral Nerve Society at Chateau Mont-Ste-Anne, Québec, June 29, 2015.

Lang M, Treister R, Oaklander AL. Cost/Benefit of Blood Tests in Idiopathic Small-fiber Polyneuropathy (SFPN). Presented at the 2015 Annual Meeting of the American Neurological Association, Chicago, IL September 28, 2015.

Website(s) or other Internet site(s)

The collaboration website for developing the Case Definition continues to be improved and is part of an overall laboratory website that provides resources for patients, research subjects, and physicians with descriptions of small-fiber polyneuropathy, associated research, and resources. It also served as an effective recruiting tool for Veterans and patients. The site can be accessed at https://NeuropathyCommons.org .

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Anne Louise Oaklander MD, PhD
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	2
Contribution to Project:	Dr. Oaklander oversaw updates of the collaboration website and provided content to the website, maintained contact with the International collaborators and participated in meetings toward developing the Case Definition, headed the analysis and preparation of the manuscripts of IVIg efficacy which initially applied the Case Definition, and of blood test predictive value.
Funding Support:	No other funding support was used to conduct the work under this award.

Name:	Max Klein PhD
Project Role:	Co-Investigator
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	Dr. Klein maintained IRB and HRPO approval for this project. He also provided content to the collaboration website, advised on the Delphi Method, analyzed Delphi process data, initiated subject recruitment, and performed research testing and data analysis.
Funding Support:	No other funding support was used to conduct the work under this award.

Name:	Ian Farquhar BS (replaced Stephanie Ortiz BS, Emily Kaiser, and Kate O'Neil BS)
Project Role:	Clinical Studies Coordinator/Research Assistant
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	4
Contribution to Project:	Ms. O'Neil, followed by Ms. Ortiz, Ms. Kaiser, and Mr. Farquhar assisted with maintaining IRB (and HRPO) documentation, contributed content to the collaborative website, advised on the design of the secure portion of the collaborative website in accordance with the Delphi Method, assisted with recruitment, and maintained the database of study subjects.
Funding Support:	No other funding support was used to conduct the work under this award.

Name:	Heather Downs BS
Project Role:	Histotechnologist
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Ms. Downs contributed content to the collaborative website including detailed instructions on preparing skin biopsies, processed administrative activities related to this study, and assisted with recruitment.
Funding Support:	No other funding support was used to conduct the work under this award.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

There are no changes to report that impact personnel effort on this project.

What other organizations were involved as partners?

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

QUAD CHARTS: A Quad Chart is provided at Appendix 8.

9. REFERENCES

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10. ACRONYMS AND ABBREVIATIONS

A1C (a blood sugar test)
AB Antibody
ACTTION Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks
ACE Angiotensin converting enzyme
AFT Autonomic function test
ANA Antinuclear antibody
AST/ALT aspartate transaminase/ alanine transaminase
BUN Blood Urea Nitrogen
C, C3, C4 Complement components
CMI Chronic multisymptom illness
CO2 Carbon dioxide
CONCEPPT Consortium on Clinical Endpoints for Peripheral Neuropathy Trials
CWP Chronic widespread pain
DOD Department of Defense
DSDNA Anti-double stranded DNA antibody
EGFR Estimated glomerular filtration rate
EMG Electromyography
ESR Erythrocyte sedimentation rate
FDA Food and Drug Administration
GTT Glucose tolerance test
Hct Hematocrit
Hgb Hemoglobin
HRPO Human Research Protections Office
HCV Hepatitis C virus
IgA,G,M Immunoglobulin A,G,M
IRB Institutional Review Board
IVIg Intravenous Immunoglobulin
LEP Laser-evoked potential
MCH Mean corpuscular hemoglobin
MCHC Mean corpuscular hemoglobin concentration
MCV Mean corpuscular volume
MGH Massachusetts General Hospital
MPV Mean platelet volume
NCS Nerve conduction study
NIH National Institutes of Health
NRBC Nucleated red blood cells
PI Principal Investigator
Plt Platelets
QST Quantitative sensory test
RAC Research Advisory Committee
RBC Red blood cell count
RDW Red cell distribution width
REDCap The Research Electronic Data Capture platform
SFN Small-fiber neuropathy
SFPN Small-fiber polyneuropathy
SPEP/IFIX serum protein electrophoresis and immunofixation
SS-A, SS-B Sjögren's-syndrome-related antigens A, B
TSH Thyroid-stimulating hormone
TTG Tissue Transglutaminase Antibodies
USAMRMC US Army Medical Research and Materiel Command
WBC White blood cells

APPENDIX 1. Global experts participating in the Delphi process

National:

David Herrmann, MD (University of Rochester, Rochester, NY)
Ahmet Höke, MD, PhD (Johns Hopkins Hospital, Baltimore, MD)
Norman Latov, MD, PhD (Weill Cornell Medical College, New York, NY)
Glenn Lopate, MD (Washington University in St. Louis, MO)
Anne Louise Oaklander, MD, PhD (Massachusetts General Hospital, Boston, MA)
A. Gordon Smith, MD (University of Utah, Salt Lake City, UT)

International:

Colin Chalk, MD, CM, FRCPC (McGill University, Montreal, Canada)
Catharina Faber, MD, PhD (Maastricht University Medical Centre, Maastricht, Netherlands)
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APPENDIX 2. Delphi process questions and updated answers in each round

First set of questions and responses for each round so far are as follows (All of the following are out of 23 responses per question in the first round, 10 responses affirming or changing their responses in the second round, and 1 new participant). Shaded responses indicate consensus:

1. What name should be used to refer to this illness?

First round	Second round
6 SFPN (26%)	4 SFPN (17%)
16 SFN (70%)	19 SFN (79%)
1 small fiber pathology (4%)	1 small fiber pathology (4%)

2. Should we develop criteria for “definite”, “probable”, and “possible” cases?

First round	Second round
22 yes (96%)	(not included in the re-vote; no re-vote necessary)
1 no (4%)	

3. Should this group develop separate diagnostic criteria for clinical vs. research purposes?

First round	Second round
11 yes (48%)	10 yes (42%)
12 no (52%)	14 no (58%)

4. Which demographic data are important to collect when diagnosing small-fiber (poly)neuropathy? Check all that apply.

	First round	Second round
Age	23 (100%)	23 (96%)
Sex	23 (100%)	23 (96%)
Race	17 (74%)	18 (75%)
Ethnicity	14 (61%)	17 (71%)

5. Which diagnostic tests should this group recommend when diagnosing small-fiber (poly)neuropathy? Check all that apply.

	First round	Second round
Electromyography (EMG)	7 (30%)	6 (25%)
Nerve conduction studies (NCS)	17 (74%)	18 (75%)
Distal leg skin biopsy immunolabeled against PGP9.5	21 (91%)	23 (96%)
Quantitative sensory testing (QST)	12 (52%)	12 (50%)
Somatosensory evoked potentials (SSEP)	4 (17%)	4 (17%)
Laser evoked potentials (LEP)	5 (22%)	4 (17%)
Composite autonomic function testing (AFT)	17 (74%)	17 (71%)
--Heart rate variability during	17 (74%) *	(In this round, the

deep breathing		four individual AFT sub-tests were removed, and only "Composite AFT" was included for clarity)
--Heart rate and blood pressure responses to Valsalva	17 (74%) *	
--Heart rate and blood pressure responses to tilt	17 (74%) *	
--Quantitative sweat testing	17 (74%) *	

* includes responses that included either the individual sub-test or Composite AFT which includes the individual sub-tests

6. Do you wish to continue to participate?

First round	Second round
23 (100%)	24 (100%)

7. Do you have any conflicts of interest?

First round	Second round
2 yes (9%)	2 yes (8%)
21 no (91%)	22 no (92%)

7a. Please describe any conflicts of interest.

(One respondent has commercial interest in a company that processes skin biopsies; another has commercial interest in multiple sclerosis treatment and IVIg treatment laboratories)

The second set of questions and first round responses so far are as follows (All of the following are based on 24 respondents per question (as of 6 June 2017)):

"What are the most important parts of the neuro exam to include when examining a patient for possible small-fiber (poly)neuropathy?"

1. Pupils

	Important	Not important
Normality of pupil size relative for age and ambient light	12 (50%)	12 (50%)
Normality of constriction to bright light	18 (75%)	6 (25%)

2. Appearance of lower legs, feet, hands

	Important	Not important
Hair loss	15 (63%)	9 (38%)
Skin hyperperfusion (red, purple, dusky)	21 (88%)	3 (13%)
Skin hypoperfusion (white, gray)	18 (75%)	6 (25%)
Edema	17 (71%)	7 (29%)
Muscle atrophy	19 (79%)	5 (21%)

High arches	16 (67%)	8 (33%)
Hammertoes	15 (63%)	9 (38%)
Fasciculations	12 (50%)	12 (50%)
Thin, shiny atrophic skin	19 (79%)	5 (21%)
Skin excoriations or ulcers (trauma to itchy or painless areas)	21 (88%)	3 (13%)
Amputations	20 (83%)	4 (17%)

3. Motor function

	Important	Not important
Strength of great toe extension	18 (75%)	6 (25%)
Strength of finger extension	17 (71%)	7 (29%)

4. Sensory function

	Important	Not important
Joint position – great toe	21 (88%)	3 (13%)
128 Hz vibration – great toe	21 (88%)	3 (13%)
Light touch – legs, feet, toes	20 (83%)	4 (17%)
Pin sharpness– legs, feet, toes	24 (100%)	0 (0%)

5. Reflexes

	Important	Not important
Ankle jerks as compared to other reflexes such as at knees	20 (83%)	4 (17%)

APPENDIX 3. Application of SFPN criteria to evaluate efficacy of IVIg for treatment of SFPN in *Therapeutic Advances in Neurological Disorders*

Ther Adv Neurol Disord
1–12
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IVIg for apparently autoimmune small-fiber polyneuropathy: first analysis of efficacy and safety

Xiaolei Liu, Roi Treister, Magdalena Lang and Anne Louise Oaklander

Abstract

Objectives: Small-fiber polyneuropathy (SFPN) has various underlying causes, including associations with systemic autoimmune conditions. We have proposed a new cause; small-fiber-targeting autoimmune diseases akin to Guillain-Barré and chronic inflammatory demyelinating polyneuropathy (CIDP). There are no treatment studies yet for this 'apparently autoimmune SFPN' (aaSFPN), but intravenous immunoglobulin (IVIg), first-line for Guillain-Barré and CIDP, is prescribed off-label for aaSFPN despite very high cost. This project aimed to conduct the first systematic evaluation of IVIg's effectiveness for aaSFPN.

Methods: With IRB approval, we extracted all available paper and electronic medical records of qualifying patients. Inclusion required having objectively confirmed SFPN, autoimmune attribution and other potential causes excluded. IVIg needed to have been dosed at ⩾1 g/kg/4 weeks for ⩾3 months. We chose two primary outcomes – changes in composite autonomic function testing (AFT) reports of SFPN and in ratings of pain severity – to capture objective as well as patient-prioritized outcomes.

Results: Among all 55 eligible patients, SFPN had been confirmed by 3/3 nerve biopsies, 62% of skin biopsies, and 89% of composite AFT. Evidence of autoimmunity included 27% of patients having systemic autoimmune disorders, 20% having prior organ-specific autoimmune illnesses and 80% having ⩾1/5 abnormal blood-test markers associated with autoimmunity. A total of 73% had apparent small-fiber-restricted autoimmunity. IVIg treatment duration averaged 28 ± 25 months. The proportion of AFTs interpreted as indicating SFPN dropped from 89% at baseline to 55% ($p \leqslant 0.001$). Sweat production normalized ($p = 0.039$) and the other four domains all trended toward improvement. Among patients with pre-treatment pain ⩾3/10, severity averaging 6.3 ± 1.7 dropped to 5.2 ± 2.1 ($p = 0.007$). Overall, 74% of patients rated themselves 'improved' and their neurologists labeled 77% as 'IVIg responders'; 16% entered remissions that were sustained after IVIg withdrawal. All adverse events were expected; most were typical infusion reactions. The two moderate complications (3.6%) were vein thromboses not requiring discontinuation. The one severe event (1.8%), hemolytic anemia, remitted after IVIg discontinuation.

Conclusion: These results provide Class IV, real-world, proof-of-concept evidence suggesting that IVIg is safe and effective for rigorously selected SFPN patients with apparent autoimmune causality. They provide rationale for prospective trials, inform trial design and indirectly support the discovery of small-fiber-targeting autoimmune/inflammatory illnesses.

Keywords: autoimmune diseases, dysautonomia, immunotherapy, intravenous immunoglobulin, neuropathic pain, peripheral nervous system diseases

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Introduction

The polyneuropathies involve widespread damage to the body's peripheral nerves. 'Small-fiber polyneuropathy' (SFPN), also known as small-fiber neuropathy, refers to those polyneuropathies that preferentially affect peripheral neurons with the

thinnest axons, including the unmyelinated C-fibers, thinly myelinated A-δ somatosensory axons and the sympathetic and parasympathetic neurons. In the past, these were dichotomized as somatic *versus* autonomic, but immunohistochemical studies blurred the distinction, revealing non-sensory functions of 'somatosensory' axons including innervation and control of sweating, small blood vessels and bone.[1,2] Careful evaluation showed that most patients with somatosensory complaints such as neuropathic pain, itch or sensory loss also have autonomic involvement,[3] hence the current tem 'small-fiber polyneuropathy'. Applying the only population-based estimate, 52.95/100,000[4] yields an estimated 2017 global prevalence approaching four million. This is an underestimate, since it required neurologists' confirmation, whereas most patients remain undiagnosed. Given recent reports that SFPN underlies 40% of the fibromyalgia syndrome,[5,6] there could there could conceivably be more than 100 million cases worldwide.

Small-fiber neurons' multifunctionality explains why SFPN increases risk of multiple symptoms. The most common are chronic widespread pain and/or itch,[7] postural hypotension and/or tachycardia (POTS),[8] nausea, constipation and/or diarrhea, disordered sweating, followed by urological and sexual dysfunction. Recent studies suggest that SFPN is also associated with symptoms traditionally thought to originate in the brain, including chronic headaches and cognitive concerns.[9,10] SFPN can even cause abnormal brain blood flow and functional connectivity that might contribute to the 'brain fog' some patients report.[11]

Given these many symptoms, it can be ineffective to treat only with symptom palliation. The polypharmacy that often ensues is expensive and can cause side effects. The use of opioids to manage chronic pain has been particularly problematic. Identifying and remediating the specific medical cause in each patient is a better strategy. Small-fiber axons grow throughout life, so curtailing ongoing damage can permit them to regenerate to their varied targets. One treatment can improve and sometimes improve or resolve multiple symptoms and dysfunctions.

Because small-fiber axons are long and thin, they are vulnerable to disruptions in axon maintenance by any medical problem, and SFPN has more than a dozen medical causes.[12] Diabetes, the most common cause in developed countries, is estimated to cause half of small-fiber predominant neuropathy.[13] The second largest group of SFPN patients, estimated at 20–50%,[4,14–17] comprises patients with no apparent cause at first evaluation; so-called 'cryptogenic' or 'initially idiopathic' SFPN (iiSFPN). Ameliorating or curing diabetes mitigates complications including neuropathy,[18] as do disease-modifying treatments for nutritional, toxic and infectious causes, but there are no options for the 30–50% of patients with iiSFPN.

We and others have suggested that autoimmunity and inflammation play a far greater role in iiSFPN than recognized. Systemic autoimmune conditions linked to SFPN include lupus, rheumatoid arthritis, sarcoidosis, vasculitis and celiac.[19–35] Sjögren's is the most common among these Virtually nothing is known about how systemic autoimmune diseases affect small fibers.[36–38]

We have proposed a new cause of iiSFPN – autoimmunity specifically targeting small-fiber epitopes. Given the current lack of proof, we call this 'apparently autoimmune' SFPN (aaSFPN). This concept is biologically plausible, akin to the well-characterized acute and chronic large-fiber-targeting autoimmune diseases Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor mononeuropathy (MMN).[39,40] The current very limited evidence about mechanisms suggests that autoantibodies and complement consumption[3,12] are more important than cytotoxic T-cell attack. This discovery has important implications for medical care, given the prevalence and disability of SFPN, and the widespread availability and proven efficacy of old and new immunotherapies for autoimmune neuropathies.

The concept of aaSFPN began with reports of a few iiSFPN patients who responded to treatment with corticosteroids or pooled human intravenous immunoglobulins (IVIg).[41–44] The first case series found corticosteroids efficacious in 10/15 SFPN patients (67%), with improvement in symptoms plus objective tests.[3] Since prolonged corticosteroids can cause complications, IVIg is increasingly prescribed off-label for aaSFPN. It is a first-line treatment for GBS, CIDP, and MMN[45–48] that modifies B- and T-cells, inhibits antibody production and interferes with the complement cascade. Most nerve specialists know how to manage IVIg, and dosing parameters were established in trials such as the Immune Globulin Intravenous

CIDP Efficacy (ICE) trial, a large double-blind, placebo-controlled, randomized crossover trial.[49] In addition to confirming efficacy, these trials established the safety outcomes and dosing algorithms we applied here.[50,51]

All of the earlier small series document favorable outcomes from IVIg treatment of SFPN, for instance in three patients with associated celiac,[52] three with sarcoidosis,[53] and six with Sjögren's syndrome.[54,55] In our case series of early-onset SFPN, 5/8 (62%) improved clinically with early evidence of improved skin biopsies and AFT.[3] A multicenter, double-blind trial of IVIg in 23 patients with eosinophilic granulomatosis with polyangiitis (Churg-Strauss) reported efficacy for pain, a secondary outcome.[56]

However, supplies of IVIg are limited, administration is difficult and yearly cost can exceed $100,000, so insurers do not usually pay for treatment of SFPN. Plus, IVIg often causes infusion reactions and rarely causes serious adverse events.[57] Systematic studies are needed, and the first randomized, double-blind, placebo-controlled, clinical trial of IVIg for idiopathic small-fiber neuropathy has begun recruitment in Europe.[58] However, interim data are urgently needed now to guide clinical practice and reimbursement decisions.

To gain insights from currently available data, we performed structured abstraction from medical records to generate the first large case series for analysis. We chose change in pain severity as a primary outcome because chronic pain is arguably the most disabling symptom of SFPN and one of great concern to patients. Plus, validated patient-reported pain scores were routinely collected.[59] However, pain is a subjective patient-reported outcome that is highly susceptible to placebo effects, so we judged it prudent to include an objective outcome that could not be influenced by patient expectations. The strongest candidates were PGP9.5-immunolabeled skin biopsies from the lower leg and composite autonomic function testing (AFT), which have been endorsed for diagnosing SFPN by major neurological societies.[60,61] We selected AFT given the high prevalence of potentially dysautonomic symptoms in SFPN, recommendations to measure autonomic as well as somatic dysfunction when assessing small-fiber neuropathies[62] and prior use of AFT in assessing systemic autoimmune SFPN.[31] For secondary outcomes, we extracted all safety data, demographic data, relevant blood-test results, plus patients' and physicians' impressions of change, all generally reported in treatment trials. So far as we know, this is the first systematic study of IVIg treatment for 'idiopathic' SFPN.

Methods

Standard protocol approvals, registrations and patient consents

All protocols were approved by the hospital's IRB, which waived informed consent.

Study design, case definitions and baseline patient characteristics

Since there are no consensus case definitions, to identify potential subjects we screened the records of every patient evaluated for SFPN in our hospital-based peripheral-nerve practice since our index case[42] through 31 December 2015 and developed rigorous research-oriented preliminary case definitions for SFPN, for iiSFPN and for aaSFPN.

Inclusion required meeting our case definition of 'definite SFPN', which required physician's clinical diagnosis plus objective confirmation of diagnosis by distal-leg PGP9.5-immunolabeled skin biopsy, surgical nerve biopsy or AFT. Since these studies had been performed in diverse facilities, to add rigor we accepted only original reports and interpretations from JC-accredited clinical labs using standard approved methods and analyses. Skin biopsy diagnosis required density of epidermal nerve fibers below the fifth centile of predicted.[60,61] For nerve biopsies, diagnosis requires qualitative or morphometric evidence of reduced unmyelinated and/or thinly myelinated axons, prior axonal degeneration in the form of empty Schwann cell stacks, collagen pockets, and sometimes excess inflammatory cells and clusters of regenerating axons.[43,60,63,64] Diagnosis by composite AFT requires appropriate abnormalities in $\geqslant$2/4 domains: heart rate variability during deep breathing (HRDB); heart and blood-pressure responses to Valsalva maneuver and to vertical tilt; and quantitative sudomotor axon reflex testing (QSART).[60,65]

For inclusion, patients also had to meet the case definition of apparently autoimmune SFPN (aaSFPN) we developed. In addition to definite SFPN, this required systematic exclusion of non-immune

causes by medical history, exam and results of recommended blood tests.[12] We routinely evaluated for diabetes, prediabetes, thyroid disorders, abnormal vitamin levels, Sjögren's, celiac, hepatitis, Lyme disease and monoclonal gammopathies, plus less-common potential causes suggested by individual histories or examinations. Then it required objective evidence of dysimmunity.

We currently recognize two types of aaSFPN: that associated with systemic autoimmunity (either a recognized systemic inflammatory condition, or evidence of more than one organ-specific condition); and autoimmunity apparently restricted to small fibers. For patients to be classified with systemic rheumatologic disorders, we preferred a rheumatologist's consultation. For diagnoses of organ-specific autoimmune disorder (e.g. Hashimoto's thyroiditis), we preferred diagnoses made by a primary care provider or appropriate subspecialist using accepted clinical criteria. Our case definition of 'systemic aaSFPN' thus required having no other apparent cause of neuropathy, plus either a systemic rheumatologic disorder, or autoimmune disease affecting at least one other organ system.

Classification of a patient as having nerve-specific aaSFPN was more speculative, and rheumatologists were often consulted. This case definition also required no other apparent cause of neuropathy, no systemic rheumatologic diagnosis, plus objective supporting evidence including inflammatory infiltrates within nerve or skin biopsies. Persistent, otherwise unexplained blood-test markers of dysimmunity/inflammation were also accepted. These comprised antinuclear antibodies (ANAs, conservatively defined as $\geqslant$1:160 dilution), elevated erythrocyte sedimentation rate (ESR; $\geqslant$15 mm/h), low complement component 4 (C4; $<$20 mg/dl), low complement component 3 (C3; $<$85 mg/dl) and Sjögren's autoantibodies (SSA/Ro, SSA/La). In addition to pathology and serology, we also accepted clear improvement in neuropathy from prior immunotherapy, as in our index case.[42]

The additional requirement for study inclusion was an adequate trial of IVIg, specifically treatment initiated at doses $\geqslant$1 g/kg/4 weeks, the standard for autoimmune neuropathies.[45] For efficacy analyses, patients had to have been treated for at least 3 months. The safety analysis included every patient regardless of treatment duration.

Data collection

The variables extracted and analyzed were demographics, medical histories, results of blood tests for neuropathy causes, pain severity ratings, interpretations of composite AFT and individual domain parameters, details of IVIg dosing, adverse events (AEs), patients' global impression of change (PGIC), physicians' assessment of benefit and detailed analyses of all safety events and treatment discontinuations.

The first primary outcome was pain severity, rated at each visit with the standard 11-point numeric scale, with 0 representing 'no pain' and 10 'worst pain'.[59] The primary analysis included all patients with baseline pain $\geqslant$3/10. The post-treatment pain scores reported are the mean of all available pain scores gathered during treatment. The other co-primary outcome was the reported clinical interpretation of AFT results as diagnostic of SFPN.

The secondary outcomes were: (1) safety – all AEs or infusion reactions were abstracted and rated as mild, moderate or severe according to guidelines;[66] (2) standard demographic characteristics; (3) pertinent medical histories and results of diagnostic testing; and (4) the standard seven-point PGIC.[67] The clinic routinely collected the PGIC, using these instructions: 'Based on your own impression, please check the best description of the overall change in your illness in the last month. Score this regardless of what you think caused the change.' Response items ranged from 1 ('my illness is very much better') to 7 ('my illness is very much worse'), with 4 representing 'there has been no change in my illness'. Secondary outcome 5 was physicians' impression of whether patients were IVIg 'responders' or 'non-responders' as extracted from their notes. Outcome 6 – treatment duration – reflected not only the balance of positive and negative effects, but often the availability of insurance reimbursement. Outcome 7 comprised reasons for any treatment discontinuation.

Statistical analyses

The SPSS for Windows version 19 package (SPSS Inc., Chicago, IL, USA) was used. The Shapiro–Wilk test established that pain ratings were normally distributed so parametric two-tailed t tests were used. Means $\pm$ standard deviations described central tendencies. McNemar tests were used for paired nominal data such as

within-subject repeat AFT interpretations. Chi-square tests compared categorical variables. Tests were considered significant at $p \leqslant 0.05$, although a Bonferroni correction was applied for determining evidence of treatment efficacy. Because there were two primary outcomes, $p \leqslant 0.025$ was required for statistical significance.

Results

Cohort characteristics

A total of 78% of the subjects (43/55) identified as female. Their age at baseline averaged 41 ± 17 years (range 6–85 years). At baseline, reports from 89% (39/44) of their AFTs, 61% (31/49) of their distal-leg skin biopsies and 3/3 sural nerve biopsies supported a diagnosis of SFPN. Among the four AFT domains, QSART sweat production, considered most specific for SFPN, was the one most often abnormal, in 69% of patients. Among the 17 patients with skin biopsies interpreted as normal and baseline AFT results available, 88% had abnormally reduced sweating. A total of 60% (33/55) had had their SFPN confirmed by one test; it had been confirmed by two tests in 38% (21/55); and 2% (1/55) had confirmation from all three tests. The latency between onset of SFPN symptoms to start of IVIg treatment averaged 6.3 ± 6.3 years (range 0.3–33 years). A total of 35% of patients had received Gammagard, 38% had received Gamunex, 6% had received Privigen and 4% had received Gammaked. Doses during the first 3 months of treatment ranged between 1.3–2.0 g/kg/4 weeks, after which doses were usually slowly titrated downwards in patients who continued treatment.

Regarding the attribution of SFPN to autoimmune causes, 27% (15/55) of these patients had systemic autoimmune diagnoses. Eight had been diagnosed with Sjögren's syndrome, four with systemic lupus erythematosus, two with rheumatoid arthritis and one with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). A total of 20% (11/55) had other organ-specific autoimmune conditions, specifically five with Hashimoto's thyroiditis, three with inflammatory bowel diseases and one each with type 1 diabetes, Grave's disease and psoriasis. Regarding serologic markers suggestive of autoimmunity, 80% (45/56) of patients had one or more abnormal blood-test result consistent with dysimmunity. Specifically, 35% had ANAs (⩾1:160 dilution), 33% had elevated ESR (⩾15 mm/h), 28% had low C4 (<20 mg/dl), 14% had low C3 (<85 mg/dl) and 11% had Sjögren's autoantibodies (SSA/Ro, SSA/La). Additionally, 28% had IgG deficiency (IgG <614 mg/dl), 18% had IgG subclass deficiency, 14% had IgM deficiency (IgM <53 mg/dl) and 11% had IgA deficiency (IgA <69 mg/dl).

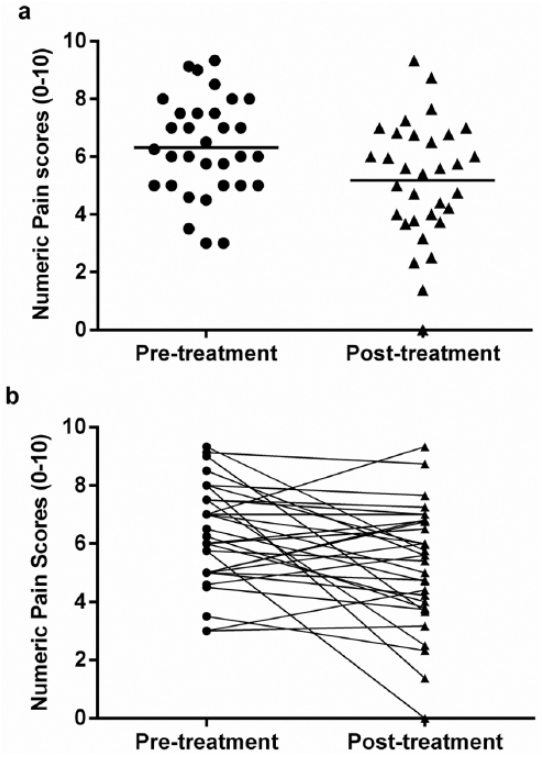

Figure 1. Pain scores before and during IVIg treatment. (a) Circles represent pain scores before treatment, triangles represent pain scores during IVIg treatment and lines represent group averages. (b) Each individual patient's change in pain scores.

Primary (efficacy) outcomes

Four subjects discontinued IVIg within the first 3 months of treatment because of infusion reactions, so the efficacy sample comprised 51 patients. As shown in Figure 1, among the 32 with baseline pain ⩾3/10, baseline pain severity averaging 6.3 ± 1.7 dropped to 5.2 ± 2.1 during treatment ($t = 2.875$; $p = 0.007$). A total of 31% (10/32) had ⩾30% reduction in pain, with their scores dropping on average 3.9 ± 1.9 points. As shown in Figure 2, among all 35 patients with pre- and post-treatment AFT results available, the proportion with AFT results that had been interpreted as indicating SFPN dropped from 89% (31/35) at baseline to 57% (20/35;

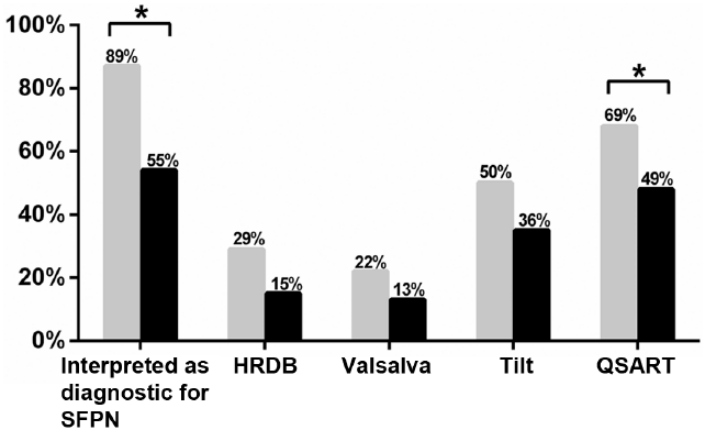

Figure 2. Prevalence of abnormal results of composite autonomic function testing (AFT).
Gray bars represent the percentage of patients with abnormal results at baseline before IVIg treatment. Black bars represent the percentage of patients with abnormal results during treatment. * represents $p < 0.05$.

$p = 0.026$) during treatment, a 31% response rate. Among the four autonomic domains tested, QSART improved significantly ($p = 0.039$). The other AFT subtests showed non-significant trends toward improvement. Thus, both of the study's two primary outcomes provided congruent evidence of efficacy.

Secondary outcomes

Safety. A total of 75% (41/55) of patients reported a treatment-incident AE. Among these, 65% (36/55) were typical transient infusion reactions. Specifically 60% reported headache, 35% reported nausea, 35% reported influenza-like symptoms and 20% reported stiff neck. These led three patients to stop IVIg before completing the intended 3-month trial. Of note, one later retried IVIg, tolerated it well and reported benefit, but the outcome of this second trial was not included in the analysis. Most infusion reactions were effectively managed using standard strategies – for example, slowing infusion rates, augmenting hydration and administering standard co-medications. There were two moderate AEs (3.6%), which were both vein thromboses (DVT), a known complication of IVIg.[68] Neither caused embolic complications. One clot developed in a subclavian vein containing an indwelling catheter placed for access. That patient continued IVIg after co-administration of warfarin followed by aspirin. The other developed in an arm vein used for peripheral administration of IVIg. It did not require discontinuing IVIg or any specific treatment. There was one serious AE (1.8%), which was new hemolytic anemia that resolved after transfusion and discontinuing IVIg. Hemolytic anemia is a known complication of IVIg.[57,69–71]

Patients' and physicians' impressions of change

Analysis of standard seven-point PGIC scores indicated that 3% (1/31) of patients rated themselves as 'very much improved', 39% (12/31) as 'much improved', 32% (10/31) as 'mildly improved', 16% (5/31) as 'unchanged', 3% (1/31) as 'slightly worse', and 7% (2/31) as 'much worse'. None rated themselves as 'very much worse'. Overall, 74% (23/31) rated themselves as improved and 10% (3/31) as worse. Physicians labeled 77% (39/51) of patients as 'IVIg responders' and 23% (12/51) as 'non-responders'. Males were more often responders than females (100% *versus* 63%; $p = 0.009$). A total of 16% of patients (8/51) experienced such profound improvement that they were able to wean and then discontinue IVIg while maintaining benefit. They had been in remission for 20 months on average as of 31 December 2015.

Treatment duration and discontinuations

Through 31 December 2015, the average duration of IVIg treatment was 27 ± 25 months (range 1–114 months; Figure 3). The 39 'responders' were treated on average for 38 ± 23 months (range 3–114 months). Twenty-nine had continued IVIg with gradual improvement and eight had stopped IVIg after remission. In two others, insurers withdrew approval for reimbursement despite documented improvement and patients'

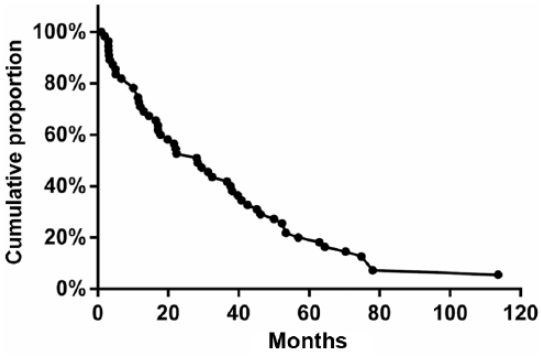

Figure 3. Duration of IVIg treatment.

desire to continue treatment. Among the 13 non-responders, eight had discontinued IVIg by 31 December 2015 because of ineffectiveness or insufficient effectiveness to justify continuing, and three because of infusion reactions.

Discussion

This first systematic study of IVIg treatment of SFPN met the overall (combined) study criteria for efficacy, plus both of the two complementary primary efficacy outcomes. All seven secondary outcomes provided additional evidence of efficacy and safety. Patients and physicians each rated 3/4 of patients as improved, and 16% of patients entered sustained remission that permitted IVIg withdrawal. The profile of AEs was similar to prior reports.[72] Together, these results provide proof-of-concept and preliminary rationale for medical use of high-dose IVIg therapy in rigorously selected patients with confirmed SFPN attributed to autoimmunity (aaSFPN). They also imply that aaSFPN may be far more common than appreciated, and they provide strong evidence that medical insurers should no longer reflexively decline to pay for IVIg treatment of aaSFPN.

This study generated insights. First, three-quarters of the included patients were classified with 'restricted' small-fiber autoimmunity, with only one-quarter having systemic autoimmune diagnoses. Of note, one-third of all Sjögren's cases have an initial neurologic presentation.[73] Some of our participants later received systemic diagnoses, but most did not during the study. This supports our hypothesis of small-fiber-targeting autoimmunity, and suggests it may be a common cause of iiSFPN. Plus it demonstrates the need to formalize case definitions for SFPN and aaSFPN. These are prerequisites for clinical trials and basic research into mechanisms and identification of small-fiber epitopes. This study also generated the first remission rate for aaSFPN; 16% after IVIg treatment. We are not aware of prior remission rates for any type of SFPN, much less for aaSFPN, so remissions cannot be definitively ascribed to IVIg without comparator data from observational natural history studies that include untreated patients.

The blood-test analyses also were informative. The fact that 80% of patients had at least one abnormal result consistent with dysimmunity supports clinical use of these tests. Since these abnormalities helped support the decision to administer IVIg, and thus inclusion in the study cohort, there is circular reasoning. However, we earlier reported similar prevalences (28% with high ANA, 28% with high ESR, 16% with low C4, 11% with low C3 and 9% with Sjögren's serologies) among an unselected group of 195 patients with confirmed iiSFPN from all causes.[12] Also, as far as we know, these results are the first association of aaSFPN with immunoglobulin deficiency. It was unexpected to find 28% with IgG deficiency, 18% with IgG subclass deficiencies, 14% with IgM deficiency and 11% with IgA deficiency. It is unknown whether these were primary or secondary, whether genetic or autoimmune, but if confirmed, this additionally links B-cell dysfunction with aaSFPN.

One strength is this study's exploratory use of two complimentary primary outcomes, both of which improved significantly. This allowed one study to encompass both the somatic and autonomic aspects of SFPN and to balance patient-reported and objective/functional measures. Including an objective outcome meant that benefits could not be ascribed only to placebo. Given the lack of one universal symptom of SFPN, this study supports use of multiple efficacy outcomes. Although not all participants had chronic pain, this seems essential to capture given its prevalence, associated disability, and the relative inefficacy and serious adverse effects of long-term use of pain-relievers. Another strength is that all subjects had objective confirmation of diagnosis. We consider this necessary for long-term immunomodulation, given the non-specificity of SFPN symptoms and the expense and potential adverse effects of immunotherapies. However, we seek less expensive and more practical objective biomarkers.

This study's major limitation is that it is a retrospective study that provides only Class IV evidence.[74] An inherent limitation in 'real-world' studies is variation in dosing and assessment parameters. Here, the initial target dose was 2.0 g/kg/4 weeks, as in all five major placebo-controlled trials of IVIg for CIDP.[49,75–78] We and others find it more efficient to trial the highest recommended dose, and then titrate downwards, rather than to try low doses that, if ineffective, often engender retrials of higher doses.[51] Other potential contributors to dosing variability included potentially inaccurate patient weights, rounding doses and dose individualizations for reasons including tolerability. The actual initial doses, all 1.3–2.0 g/kg/4 weeks, were within the range used in clinical trials for CIDP,[45] and similar to the mean 1.4 ± 0.6 g/kg/4.3 weeks dose optimal for CIDP and MMN.[51] Another study strength is that patients were treated for at least 3 months before assessing efficacy, as single-dose trials are now considered insufficient. Lastly, to facilitate data aggregation patients were reassessed at standard intervals; 3 months for initial prescriptions or after dose changes, and 6 months after same-dose refills.

Although IVIg was initially prescribed in 4-week cycles (from day 1 of each infusion), actual infusion days sometimes varied. Cycle length was sometimes shortened to resolve end-of-cycle wearing off and during tapering, sometimes cycle lengths were increased to 5–6 weeks. These intervals correspond well to the 4.3 week mean cycle length reported in optimized CIDP and MMN patients.[51] We always reported doses in g/kg/4 weeks to control for cycle length. The parameters used here may inform medical use as well as trial design.

How do the efficacy and safety results compare to those reported in other immune polyneuropathies? The large IVIg trials for large-fiber demyelinating polyneuropathy had similar response rates; 53% in CIDP,[79] 53% in GBS[80] and 78% in MMN.[48] The current study's safety profile also compares well to published data.[81] The 60% prevalence of infusion reactions here corresponds favorably to 75–77% prevalence elsewhere.[49,82] The one serious AE, hemolytic anemia, is established, with incidence ~1 per 1000 IVIG treatment episodes,[57] and the 1.8% prevalence of DVT here compares well to the 11.3% rate in the one large study of thromboembolic complications of IVIg for neuropathy.[68]

This study helped us develop interim case definitions and treatment guidelines that may be useful clinically. *Definite SFPN* requires a physician's impression based on history and exam plus objective confirmation from a consensus-recommended objective test. *Apparently autoimmune SFPN* requires systematic exclusion of non-immune causes including with blood tests,[12] plus evidence of autoimmune association. *Systemic aaSFPN* requires diagnosis (prior or concurrent) of a neuropathy-associated rheumatologic disorder. In patients without systemic autoimmunity, diagnosing *small-fiber restricted aaSFPN* requires blood-test or pathological evidence of dysimmunity/inflammation, or prior response to immunotherapy.

Additional considerations in selecting candidates for IVIg include (1) physician impression that the aaSFPN is disabling and not improving; (2) no substantial improvement from no treatment or conventional treatment of symptoms; (3) no contraindications to IVIg; and (4) patient preference. Until trial results are published, this study provides rationale for appropriate medical prescribing and insurer coverage of repeated high-dose immunoglobulin treatment for carefully selected patients with apparently autoimmune small-fiber polyneuropathy.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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APPENDIX 4. Poster presented at the 2015 Meeting of the Peripheral Nerve Society

COST/BENEFIT ANALYSIS OF BLOOD TESTS FOR CAUSES OF "IDIOPATHIC" SMALL-FIBER POLYNEUROPATHY (SFPN)

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BACKGROUND

SFPN is a common and often disabling type of polyneuropathy. The common symptoms are sensory and dysautonomic, reflecting dysfunction of small-diameter unmyelinated and thinly myelinated peripheral neurons. Objective testing for SFPN is offered to patients with symptoms but no known causes (idiopathic). For this purpose, neurological societies recommend distal-leg skin biopsy measurements of small-fiber epidermal innervation, autonomic function testing (AFT) of cardiovagal, adrenergic, and sudomotor small-fiber function, and nerve biopsy in select cases.[1,2] If these confirm SFPN, blood testing is recommended to look for occult causes.[3] Testing is recommended for diabetes, dysthyroidism, low vitamin B12, paraproteinemia, celiac, Sjögren's, sarcoidosis, and autoimmunity. Potential infectious causes include HIV, hepatitis C, and leprosy and Lyme in some locations. The diagnostic utility of each specific test is unclear despite several studies,[4,5,6] and cost has only recently been considered.[7]

To evaluate diagnostic utility of commonly available neuropathy-related blood tests in patients with idiopathic SFPN and formulate evidence-based recommendations for testing in this setting we surveyed yield and cost of 21 blood tests in a large cohort with objectively confirmed predominantly idiopathic SFPN in the northeastern United States (New England).

METHODS

***Study design*: All patients with abnormal test results that objectively confirmed the presence of SFPN at MGH during calendar year 2013 were considered for inclusion. The tests reviewed were distal-leg skin biopsy, autonomic function testing (AFT) and surgical nerve biopsy.[1] Patients also had to have at least one blood-test result available. IRB permission was obtained.**

***Blood tests studied*: All commonly available 21 blood tests reported in the literature as useful for identifying causes of SFPN were studied (Table 1). Results from within one year before or after testing for SFPN were included. For repeated tests, the result from closest to the date of neuropathy testing was used.**

***Cohort characteristics*: Data regarding the most common symptoms of SFPN were collected from medical records to further characterize this cohort. Results of electromyography and nerve conduction studies (EMG/NCS) were also recorded.**

***Statistical analyses*: SPSS for Windows version 19 (Chicago, IL) was used. Relationships between age, gender, and the prevalence of abnormal results of blood tests were analyzed using the McNemar test. Patients were dichotomized as young or old using the median age of 49 as the discriminator. Given the explanatory nature of this study, no corrections were made for multiple comparisons.**

RESULTS & CONCLUSIONS

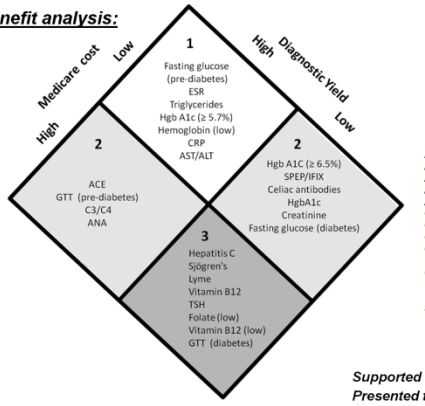
- **Review of 415 records yielded 195 qualifying patients referred by 29 physicians.**
- **Patients were 70% female, 95% Caucasian, mean age 43.0 ± 18.6 years; 147 had SFPN confirmed by skin biopsy, 42 by AFT and 6 by nerve biopsies.**
- **Overall, 57% of patients had ≥ 1 abnormal blood-test result, among those with ≥ 10 tests, 91% had ≥ 1 abnormal result.**
- **The most prevalent blood-test abnormality was high angiotensin-converting enzyme (ACE), but no patients had sarcoidosis diagnoses or diagnostic chest imaging. High ACE may be linked to SFPN pathogenesis.**
- **44% had blood-test abnormalities consistent with dysimmunity (ESR, ANA, C3, C4) suggesting possible associations and supporting routine testing.**
- **In this idiopathic SFPN cohort, the 2% prevalence of diabetes, 17% prevalence of prediabetes, and 24% prevalence of high triglycerides were less than prevalences in the general Massachusetts population.**
- **We did not find age or sex effects on test outcomes other than high triglycerides being more common in males (p = 0.026).**
- **US government (Medicare) reimbursement for all 21 blood tests was $305.73 per patient. Factoring yield and cost generated the test groups shown below. These permit cost-effective sequential testing.**

Prevalence of abnormal blood-test results (n = 195)

Test and definition of abnormal	Prevalence of abnormal results (n tested)	Rationale for test
ACE levels (high)	44.6% (83)	Sarcoidosis
2 hour value from GTT (140-199 mg/dl)	33.3% (12)	Impaired glucose tolerance (prediabetes)
Fasting glucose (100-126 mg/dl)	31.2% (16)	Impaired fasting glucose (prediabetes)
ESR (high)	28.0% (157)	Inflammation/autoimmunity
ANA (>1:160)	27.5% (153)	Autoimmunity/systemic lupus erythematosus
Triglycerides (high)	24.7% (97)	Hypertriglyceridemia
Hgb A1c (≥ 5.7%)	20.4% (108)	Recent hyperglycemia (prediabetes)
Hemoglobin (low)	18.9% (189)	Anemia
C4 (low)	15.7% (115)	Autoimmunity and vasculitis
Liver AST/ALT (high)	14.8% (162)	Alcoholism, hepatitis C
C-Reactive protein (high)	12.6% (95)	Inflammation
C3 (low)	11.0% (118)	Autoimmunity and vasculitis
Sjögren's antibodies (antiRo/SS-A, antiLa/SS-B)	9.2% (98)	Sjögren's disease
Lyme	8.7% (104)	Lyme disease
Hgb A1C (≥ 6.5%)	5.4% (111)	Recent hyperglycemia (diabetes mellitus)
SPEP/IFIX	3.9% (128)	Monoclonal gammopathy
Celiac antibodies (IgA TTG) (high)	3.5% (109)	Celiac sprue
Creatinine (high)	2.5% (162)	Chronic kidney disease/Fabry disease
Thyroid stimulating hormone (low)	2.1% (144)	Hypothyroidism
Folate (low)	2.0% (49)	Folate deficiency
Vitamin B12 (low)	1.5% (135)	Vitamin B12 deficiency
Hepatitis C antibodies	1.1% (88)	Hepatitis C
Fasting glucose (≥ 126 mg/dl)	0.0% (16)	Diabetes mellitus
2 hour glucose (≥ 200 mg/dl)	0.0% (12)	Diabetes mellitus

High: Only values above the reference range were interpreted as abnormal.
Low: Only values below the reference range were interpreted as abnormal.

Cost/benefit analysis:



Abbreviations:
ACE = angiotensin converting enzyme
ANA = antinuclear antibodies
ALT = alanine transaminase (liver function)
AST = aspartate aminotransferase (liver)
CBC = complete blood count
CRP = C-reactive protein
C3 = complement component 3
C4 = complement component 4
ESR = erythrocyte sedimentation rate
GTT = glucose tolerance test
HgbA1c = hemoglobin A1c
IFIX = serum protein immunofixation
SPEP = serum protein electrophoresis

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APPENDIX 5. Poster presented at the 2015 Meeting of the American Neurological Association

Cost/Benefit of Blood Tests in Idiopathic Small-fiber Polyneuropathy (SFPN)

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ABSTRACT

Effective treatment of SFPN requires detecting and treating its causes. Since diagnosis is difficult, symptomatic people without known cause ("idiopathic" cases) are referred for objective test confirmation of SFPN. Patients with confirmed SFPN diagnoses then undergo testing for cause. This IRB-approved study evaluated the yield and cost of 21 widely available, approved blood tests results for neuropathy causes. Inclusion required a physician's impression of SFPN, confirmation during 2013 by an AAN-recommended objective test (autonomic function testing, PGP9.5 distal-leg skin biopsy, sensory nerve biopsy), and ≥ 1 blood-test result. The primary outcomes were blood-test diagnostic yield (% abnormal results) and cost, as approximated by Medicare reimbursement rates. Reviewing 415 records yielded 195 qualifying and included patients. They were 70% female, 95% Caucasian, aged 43.0 ± 18.6 years. Tests identified potentially relevant abnormalities in 57%; most commonly high erythrocyte sedimentation rate (ESR; in 28%), antinuclear antibodies (ANA ≥ 1:160; in 27%), hypertriglyceridemia (in 25%), and low complement C4 (in 16%). 42% had ≥ 1 dysimmune marker (ESR/ANA/C4). The most prevalent abnormality was high angiotensin-converting enzyme (ACE; 45%), but no patients had sarcoidosis, so specificity must be considered. Per-patient reimbursement for all 21 blood tests was $305.73. We integrated each test's yield and cost to generate recommendations for cost-efficient sequential testing in northeastern US.

BACKGROUND

Small-fiber polyneuropathy (SFPN) causes common, subjective, and non-specific cardiovascular, gastrointestinal, and sweating complaints plus widespread chronic pain, so confirming the diagnosis in patients without known risk factors (e.g., diabetes, chemotherapy) requires objective test confirmation. If SFPN is confirmed, multiple blood tests for occult causes are recommended, but their diagnostic value is uncertain. The aim of the current study was to evaluate the diagnostic performance of the commonly available neuropathy-related blood tests in a large cohort of patients with objectively confirmed predominantly idiopathic SFPN in the northeastern United States (New England).

STUDY DESIGN & METHODS

Study design: With IRB permission, records from all patients with objectively confirmed SFPN at MGH during calendar year 2013 and at least one blood-test result available were considered for inclusion. The tests were distal-leg skin biopsy, autonomic function testing (AFT) and surgical nerve biopsy. These tests are only insurance-approved for patients without known causes ("idiopathic").
Blood tests studied: All 21commonly available blood tests reported in the literature as useful for identifying causes of SFPN were studied (Table 1). Results from within one year before or after the test for SFPN were included. For tests with multiple results, the result from closest to the date of the SFPN test was used.
Cohort characteristics: Data regarding the most common symptoms of SFPN were collected from medical records to further characterize the cohort. Results of electromyography and nerve conduction studies (EMG/NCS) were recorded.
Statistical analyses: SPSS for Windows version 19 (Chicago, IL) was used. Relationships between age, gender, and the prevalence of abnormal results of blood test were analyzed using the McNemar test. Patients were dichotomized as young or old using the median age of 49 as the discriminator. Given the explanatory nature of this study, no corrections were made for multiple comparisons.

RESULTS

- Reviewing 415 records yielded 195 qualifying patients of 29 physicians.
- They were 70% female, 95% Caucasian, with mean age 43.0 ± 18.6 years.
- 147 had had their SFPN confirmed by skin biopsy, 42 by AFT and 6 by nerve biopsies.
- Overall, 57% had ≥ 1 abnormal blood-test result.
- The most prevalent blood-test abnormality was high angiotensin-converting enzyme (ACE) in 44.6%.
- We found no age or sex effects on test outcomes other than high triglycerides being more common in males (p = 0.026).

Test and definition of abnormal	Prevalence of abnormal results (n tested)	Rationale for testing in SFPN	Cost to obtain one abnormal test result
ACE (high)	44.6% (83)	Sarcoidosis	$44.66
2 hour GTT value 140-199 mg/dl	33.3% (12)	Impaired glucose tolerance (prediabetes)	$52.73
Fasting glucose (100-126 mg/dl)	31.2% (16)	Impaired fasting glucose (prediabetes)	$17.18
ESR (high)	28.0% (157)	Inflammation/infection	$13.17
ANA (>1:160)	27.5% (153)	Lupus/rheumatic disease	$59.96
Triglycerides (high)	24.7% (97)	Hypertriglyceridemia	$31.74
Hgb A1c (≥ 5.7%)	20.4% (108)	Recent hyperglycemia (prediabetes)	$64.90
Hemoglobin (low)	18.9% (169)	Anemia	$46.72
C4 (low)	15.7% (115)	Inflammation/vasculitis	$104.33
Liver AST/ALT (high)	14.8% (162)	Alcoholism, hepatitis	$47.70
C-reactive protein (high)	12.6% (95)	Injury/inflammation	$56.03
C3 (low)	11.0% (118)	Autoimmunity and vasculitis	$148.91
AntiRo/SS-A, AntiLa/SS-B	9.2% (98)	Sjögren's syndrome	$265.87
Lyme	8.7% (104)	Lyme disease	$224.02
Hgb A1C (≥ 6.5%)	5.4% (111)	Recent hyperglycemia (diabetes mellitus)	$245.19
SPEP/IFIX	3.9% (128)	Monoclonal gammopathy	$128.21
Celiac antibodies (IgA TTG) (high)	3.5% (109)	Celiac sprue	$446.29
Creatinine (high)	2.5% (162)	Chronic kidney disease/Fabry disease	$279.60
Thyroid stimulating hormone (low)	2.1% (144)	Hypothyroidism	$1,091.90
Folate (low)	2.0% (49)	Folate deficiency	$1,003.00
Vitamin B12 (low)	1.5% (135)	Vitamin B12 deficiency	$1,360.67
Hepatitis C antibodies	1.1% (88)	Hepatitis C	$1,441.82
Fasting glucose (≥ 126 mg/dl)	0.0% (16)	Diabetes mellitus	∞
2 hour glucose (≥ 200 mg/dl)	0.0% (12)	Diabetes mellitus	∞

CONSIDERATIONS FOR CLINICAL USE

- None among the patients with high ACE had sarcoidosis diagnoses or sarcoidosis revealed by chest imaging. Thus, routine testing for ACE is not necessary in this setting.
- The 44% prevalence of blood-test abnormalities consistent with dysimmunity/inflammation (ESR, ANA, C3, C4) suggests a possible association meriting further study.
- Among these idiopathic SFPN patients, the 2% prevalence of diabetes and 17% prevalence of prediabetes were less than in the Massachusetts population (2010 census) suggesting that occult hyperglycemia is rare in this setting and costly testing for it is not necessary.
- The 24% prevalence of hypertriglyceridemia in this cohort was less than the prevalence in the census-measured Massachusetts population suggesting no specific association nor need for testing.
- **Diagnostic yield, cost, and specificity can be integrated for cost-effective screening for causality in patients with idiopathic SFPN.**

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APPENDIX 6. Publication of Task 2 blood test results in the *Journal of Neurology*

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ORIGINAL COMMUNICATION

Diagnostic value of blood tests for occult causes of initially idiopathic small-fiber polyneuropathy

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Abstract Small-fiber polyneuropathy (SFPN) causes non-specific symptoms including chronic pain, cardiovascular, gastrointestinal, and sweating complaints. Diagnosis is made from history and exam in patients with known risk factors such as diabetes, but objective test confirmation is recommended for patients without known risks. If tests confirm SFPN, and it is "initially idiopathic" (iiSFPN), screening for occult causes is indicated. This study's aim was to evaluate the 21 widely available, recommended blood tests to identify the most cost-effective ones and to learn about occult causes of iiSFPN. Records were reviewed from all 213 patients with SFPN confirmed by distal-leg skin biopsy, nerve biopsy, or autonomic-function testing in our academic center during 2013. We determined the prevalence of each abnormal blood-test result (ABTR) in the iiSFPN cohort, compared this to population averages, and measured the costs of screening subjects to obtain one ABTR. Participants were 70 % female and aged 43.0 ± 18.6 years. High erythrocyte sedimentation rate (ESR) and antinuclear antibody (ANA; ≥ 1:160 titer) were most common, each present in 28 % of subjects. The ABTR ≥3 × more prevalent in iiSFPN than in the total population were high ESR, high ANA, low C3, and Sjögren's and celiac autoantibodies. Together, these suggest the possibility of a specific association between iiSFPN and dysimmunity. ABTR identifying diabetes, prediabetes, and hypertriglyceridemia were less common in iiSFPN than in the population and thus were not associated with iiSFPN here. The six most cost-effective iiSFPN-associated blood tests—ESR, ANA, C3, autoantibodies for Sjögren's and celiac, plus thyroid-stimulating hormone—had estimated cost of $99.57/person and 45.6 % probability of obtaining one abnormal result. Angiotensin-converting enzyme was elevated in 45 %, but no patients had sarcoidosis, so this test was futile here.

Keywords Sensory polyneuropathy · Skin biopsy · Nerve biopsy · Autonomic-function testing · Immunity · Cost effectiveness

Introduction

Distal peripheral polyneuropathy is highly prevalent and often disabling. The most common complaints are sensory. Many of these patients have small-fiber-predominant polyneuropathies (SFPN), in which the unmyelinated C-fibers, A-delta fibers, and/or autonomic axons are exclusively or preferentially damaged. These thin "small-fibers" use continuous rather than saltatory conduction, and they have limited axon-transport capacity, so disruptions in energy or nutrient supply damage them preferentially. Small fibers evolved to detect and signal dangerous stimuli (transducing them as "pain" and "itch") to trigger defensive responses, and to regulate organs and tissues to optimize their function. Because of these multiple tasks, SFPN presents with varying combinations of symptoms. These include widespread chronic pain and/or itch, postural hypotension and tachycardia, nausea, constipation and/or diarrhea, and less often, urological complaints [1, 2]. Neurological examination can be unrevealing in SFPN since muscle bulk, strength, tendon reflexes, and sensations of touch, position, and vibration are usually preserved.

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Electromyography and surface nerve-conduction study (EMG/NCS) do not detect small-fiber potentials, and thus they can neither detect nor exclude SFPN. Diagnosing SFPN can be difficult unless typical symptoms arise in patients with well-recognized causes of neuropathy. In such patients, the diagnosis and its cause are inferred from the medical history, the current symptoms, and any exam findings.

In many countries, diabetes is the most common cause of polyneuropathy [3]; it causes about half of SFPN in US population-based studies [4]. The second largest group of SFPN patients, comprising 20–50 % in recent series [3–7], have "initially idiopathic" or "cryptogenic" SFPN (here abbreviated as iiSFPN). They are the focus of the current study. The reason to try to identify undetected causes in iiSFPN patients is that peripheral axons grow throughout life, so diagnosing polyneuropathy and treating its underlying causes can spur axonal regeneration, which can improve or cure patients' symptoms. In contrast, even effective palliative treatments neither restore axons nor improve their function. They also add costs and risks including opioid abuse. Therefore, neurology organizations recommend that patients with initially idiopathic sensory polyneuropathy be screened for its common occult causes [8]. In a recent study of patients with mixed distal polyneuropathies, screening led to potentially disease-modifying management changes in 25 % [9].

Previously, objective confirmation of suspected SFPN required surgical biopsy of a sensory nerve. This is invasive, expensive, and thus only rarely performed. Today, PGP9.5-immunolabeled distal-leg skin biopsies and composite autonomic-function testing (AFT) are also endorsed by neurological societies and performed more widely, identifying increasing numbers of iiSFPN patients who need screening [10–13]. Research application of skin biopsy and AFT has suggested that SFPN appears to be a common denominator in several ill-defined syndromes that include chronic widespread pain and/or symptoms of dysautonomia. For instance, half among 152 patients with postural orthostatic tachycardia syndrome (POTS) had abnormal small-fiber mediated sweat production, meeting diagnostic criteria for SFPN [14]. In addition, among 41 patients with unexplained chronic widespread pain starting in childhood (i.e., juvenile fibromyalgia), 30 % of skin biopsies, 53 % of AFT, and 2/2 nerve biopsies were diagnostic for SFPN [15]. Multiple groups have now reported that almost half of patients with fibromyalgia have objective evidence of underlying SFPN [16–23]. Given that fibromyalgia affects 2–5 % of the world's population [24], idiopathic SFPN may be far more common than appreciated, so cost-effective screening strategies are needed. Plus, analyzing large samples of verified SFPN patients, as performed here, can inform about underlying causes and mechanisms.

Blood tests are the major way of identifying occult causes of polyneuropathy. Sensory and autonomic-predominant polyneuropathies are linked to abnormal blood-test results for diabetes [3], alcohol-related liver dysfunction [25], heavy-metal toxicity [26], deficiencies of vitamins B12 (cobalamin) and folate [27, 28], high vitamin B6 [29], hypothyroidism and hyperthyroidism [30, 31], paraproteinemia [32], sarcoidosis [33], and systemic autoimmune disorders including Sjögren's syndrome (SS) [34, 35], systemic lupus erythematosus [36], and celiac [37–39]. Infectious causes include human immunodeficiency virus [40], hepatitis C [41], leprosy [42], and Lyme disease [43]. Rare genetic variants underlie some familial and sporadic cases, with a Dutch SFPN cohort having 2.3 % prevalence of SCN9A sodium-channel mutations [7].

Insufficient screening increases the risk of missing potentially curable causes but excess screening is expensive, ineffective, and can lead to more testing, risk, worry, and cost. Thus, the sensitivity, specificity of association, and cost effectiveness of recommended blood tests should be defined to guide decisions about how to screen iiSFPN patients for causality. Table 1 summarizes the sample characteristics and tests evaluated in previous screening studies of sensory-predominant polyneuropathies. The American Academy of Neurology's 2008 systematic review of screening studies only endorsed testing blood glucose, B12 and metabolites, and serum protein electrophoresis/immunofixation (SPEP/IFIX) [8]. However, these recommendations were based on studies with varying inclusion criteria. More relied on EMG/NCS than on skin biopsy, nerve biopsy, or AFT (Table 1), meaning their conclusions apply more to large-fiber than small-fiber neuropathy. Furthermore, older studies can lose relevance due to recent health trends, including earlier detection of diabetes and prediabetes. Plus, each country and region has different prevalences of specific diseases and different testing customs, so recommendations from one place cannot be globally generalized. The current study has the advantage of having the largest sample of patients with verified SFPN. It is also among the first to compare the prevalences of abnormal blood-test results (ABTR) in neuropathy patients vs. the general population, and to consider the costs of screening neuropathy patients.

Methods

Subject selection

This retrospective study was approved by the Massachusetts General Hospital (MGH) institutional review

Table 1 Study design and prevalence of abnormal blood-test results (ABTR) in prior studies and this one

First author Location of study	Periquet Ohio/USA	Hughes London/UK	Smith Utah/USA	De Sousa New York/ USA	Devigili Italy	Bednarik Czechia	Khan Ohio/USA	Peters The Netherlands	Gallagher Michigan/ USA	Farhad New York/ USA	Lang MA/USA
Publication Year	1999	2004	2004	2006	2008	2009	2012	2013	2013	2015	2016
Population sampled	Suspected neuropathy with foot pain, normal strength	Sensory ± motor neuropathy	Suspected sensory predominant neuropathy	Suspected small-fiber neuropathy	Suspected small-fiber neuropathy	Painful sensory neuropathy	Small-fiber ganglionopathy and axonopathy	SFPN	DSP/SFPN	Mixed, referred for idopathic neuropathy	SFPN
Subjects with SFPN	44	Not tested	Not specified	62	67	51	175	88	52	40	195
Other samples studied	13 normal controls	50 normal controls		96 with normal skin biopsy	Other	47 Healthy controls	63 Small-fiber ganglionopathy		Various neuropathies		
Total sample size	117	100	138	158	124	131	238	88	225	284	195
Mean age (years)	57	66.9	63	56	60	58.5	55.1	56.9	63	64.0	43.0
Proportion female (%)	59	32	48	64	49	36	48	44	39	38	76
Study design	Prospective	Prospective	Prospective	Not specified	Retrospective	Prospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
Characterization tools											
Neuropathy symptoms	X	X	X	X	X	X	X	X	X	X	X
Medical history		X	X	X		X	X		X	X	
Family history		X	X	X		X					
Exposure to potential toxins		X		X		X					
Neurological signs on examination	X	X	X	X	X	X	X	X	X		
Quantitative sensory testing	X	X			X	X		X			
Objective diagnostic tests											
Distal leg PGP9.5 skin biopsy	X		X	X	X	X	X	X		X	X
Composite autonomic functions											X
Sural nerve biopsy	X									X	X
Electromyography/ nerve conduction	X	X	X	X	X	X	X	X	X	X	X
Laser Doppler flowmetry					X						
Laser evoked potentials					X						
Blood tests											
AlC diagnostic for diabetes		Not specified	Not specified		Not specified	Not specified				Not specified	5.5 %
A1C diagnostic for prediabetes		Not specified	Not specified		Not specified						14.7 %

Table 1 continued

First author Location of study	Periquet Ohio/USA	Hughes London/UK	Smith Utah/USA	De Sousa New York/USA	Devigili Italy	Bednarik Czechia	Khan Ohio/USA	Peters The Netherlands	Gallagher Michigan/USA	Farhad New York/USA	Lang MA/USA
Publication Year	1999	2004	2004	2006	2008	2009	2012	2013	2013	2015	2016
Fasting glucose for diabetes		Not specified	3.7 %		Not specified		Not specified				0.0 %
Fasting glucose for prediabetes		Not specified	7.5 %		Not specified	Not specified	Not specified				25.0 %
Glucose tolerance test for diabetes		Not specified	13 %	3 %	Not specified	Not specified	Not specified			9.2 %	0.0 %
Glucose tolerance test for prediabetes			2 %	6 %	Not specified	14.3 %	Not specified			16.2 %	
Random glucose for diabetes	0.0 %										
Thyroid stimulating hormone	0.0 %		0.0 %	2 %	Not specified	Not specified	10.3 %	Not specified	6.2 %	0.7 %	6.2 %
Thyroxine (T4)	0.0 %					Not specified	Not specified	Not specified	4.1 %		
Vitamin B12 (low)	0.0 %		2 %	6 %		Not specified	2.3 %			1.4 %	1.5 %
Methylmalonic acid	Not specified		Not specified	Not specified						Not specified	
Homocysteine	Not specified		Not specified	Not specified						Not specified	
Vitamin Bl										0.7 %	
Vitamin B6 (high)			Not specified					4.5 %		2.5 %	
Vitamin B6 (low)										0.2 %	
Vitamin C		Not specified									
Vitamin E	0.0 %	Not specified									
Folate			0.0 %			Not specified					2.0 %
Erythrocyte sedimentation rate	Not specified		0.0 %	Not specified					22.3 %	Not specified	28.0 %
Antinuclear antibodies (ANA)	11.0 %		3 %	Not specified		Not specified	Not specified		12.6 %		27.5 %
Extractable nuclear antigen antibodies	Not specified						Not specified		Not specified		
Anti-double stranded DNA				Not specified					4.5 %		
Anti-Smith antibodies				Not specified							
Ribonucleoprotein antibodies				Not specified						Not specified	
Sjogren's AB (SS-A/Ro, SS-B/La)	Not specified		0.7 %	Not specified	Not specified				Not specified	1.8 %	9.2 %
Celiac antibodies				6 %	Not specified		Not specified			1.4 %	3.5 %
Antineutrophil cytoplasmic AB				Not specified					12.0 %	Not specified	
Complement C3											11.0 %
Complement C4											15.7 %
Rheumatoid factor	Not specified			Not specified			Not specified		5.0 %	Not specified	
ANCA									12.0 %		
Cryoglobulins				Not specified			Not specified				
C-reactive protein				Not specified					17.0%	Not specified	12.6 %

Table 1 continued

First author Location of study Publication Year	Periquet Ohio/USA 1999	Hughes London/UK 2004	Smith Utah/USA 2004	De Sousa New York/USA 2006	Devigili Italy 2008	Bednarik Czechia 2009	Khan Ohio/USA 2012	Peters The Netherlands 2013	Gallagher Michigan/USA 2013	Farhad New York/USA 2015	Lang MA/USA 2016
Protein immunofixation	2.3 %		3 %	6 %	Not specified	Not specified	4.0 %	2.3 %		7.0 %	3.9 %
Quantitative immunoglobulins				Not specified						1.4 %	
Creatinine and/or blood urea nitrogen	0.0 %					Not specified					2.5 %
High cholesterol	28 %					70.2 %					
High triglycerides	34 %	Not specified				Not specified		1.1 %			24.7 %
Angiotensin converting enzyme				Not specified			0.0 %				44.6 %
Liver function tests	Not specified					Not specified					14.8 %
Hydroxyurea				Not specified							
Copper										Not specified	
HIV	0.0 %			Not specified		Not specified	Not specified			Not specified	
Lyme disease				10 %		Not specified	Not specified			0.3 %	8.7 %
Hepatitis A				Not specified							
Hepatitis B				Not specified		Not specified				Not specified	
Hepatitis C				Not specified	Not specified	Not specified	Not specified			Not specified	1.1 %
Syphilis	Not specified					Not specified					
Myelin-associated glycoprotein antibodies	0.0 %			Not specified	Not specified	Not specified				1.4 %	
Ganglioside antibodies	Not specified	Not specified	5.5 %	Not specified						Not specified	
Sulfatide antibodies	2.3 %			Not specified						0.30 %	
Antinerve antibodies	0.0 %	Not specified		Not specified		Not specified	Not specified			Not specified	
Paraneoplastic antibodies			Not specified			Not specified				Not specified	

A1C hemoglobin A1C, *AB* antibodies, *ANCA* antineutrophil cytoplasmic antibody, *MA* Massachusetts, *HIV* human immunodeficiency virus, *PGP9.5* protein gene product 9.5, *SFPN* small-fiber polyneuropathy

board, which waived need for consent. The sample comprised all patients with objective confirmation of SFPN at MGH during 2013. Patients were not required to have had a clinical evaluation by MGH neurologists or physicians. MGH is a major referral center for peripheral nerve tests, drawing patients from throughout the northeastern US and some from across the US and other countries. Inclusion required confirmation of SFPN by any among the widely recommended objective tests—PGP9.5-immunolabeled distal-leg skin biopsy, AFT, or nerve biopsy [12, 13]—plus at least one available blood-test result. MGH performs these tests on patients referred by physicians from any office or hospital using clinically accredited facilities and approved methods and interpretations.

Data collection

Literature searches were performed to identify all neuropathy-associated medical conditions usually identified by blood tests (Table 1). This yielded the 21 blood tests studied here. The medical records of all eligible subjects were reviewed to extract the results of all tests that had been performed within 1 year before or after the objective test that diagnosed SFPN. Official reports of external tests were included, but secondary mentions in the record were excluded because they are potentially inaccurate. If the same blood test had been repeated, the result from closest to the date of the SFPN diagnostic test was used for the analysis. Test results were extracted into a spreadsheet, and the accuracy of data entry was confirmed. The dichotomization of test results as normal or abnormal (Table 2) was based on each laboratory's reference range plus the significance of values outside the reference range for neuropathy; for instance, high B12 is not associated with neuropathy, so it was coded as "normal" for this analysis. Three diabetes-related tests were studied; hemoglobin A1C (A1C), fasting plasma glucose (FPG), and the 2-h glucose value from 75-g oral glucose tolerance testing (OGTT). Normality was interpreted according to American Diabetes Association (ADA) standards. Diabetes was defined by A1C $\geq$6.5 %, fasting glucose $\geq$126 mg/dl or 2-h OGGT value $\geq$200 mg/dl. Prediabetes was defined by A1C $\geq$5.7 and <6.5 %, fasting glucose 100–126 mg/dl, or 2-h OGTT 140–199 mg/dl. Lyme disease diagnosis required immunoblot confirmation.

The presence or absence of the following SFPN-associated symptoms was extracted from medical histories: Chronic widespread pain (using the standard definition of at least 3 months of axial, plus left and right sides, plus upper and lower body pains) [44], chronic headache [15], and other somatosensory symptoms (paresthesias and hypoesthesia). The cardiovascular symptoms encoded were otherwise-unexplained dizziness, POTS, and orthostatic hypotension. Gastrointestinal symptoms comprised otherwise-unexplained chronic nausea, vomiting, diarrhea, or constipation. Otherwise-unexplained urological, sexual, and sweating complaints were also encoded. All primary results of nerve conduction and electromyography studies were recorded. In the US, test costs vary between payers, so we estimated blood-test costs using the most common metric, the Medicare reimbursement rate, which was obtained from MGH's Medicare fee schedule.

Statistical analyses

Analyses were conducted using SPSS version 19. Group characteristics were represented by means $\pm$ standard deviations. Relationships between age (dichotomized by median) and gender and the prevalence of each ABTR were analyzed by Fisher's exact tests. The prevalence of each ABTR in the study sample was calculated and compared to the prevalence of each ABTR with the best available population data from epidemiologic surveys; ideally the National Health and Nutrition Examination Survey (NHANES) or the Women's Health Study (WHS). If US population data were not available, prevalences from similar countries were used as the comparator. Because the comparator data were not prospectively obtained, we did not calculate odds ratios, and we applied a very conservative arbitrary threshold to evaluate whether a particular ABTR might be specifically associated with iiSFPN. The prevalence of an ABTR in the iiSFPN cohort had to be $\geq$ 300 % of the prevalence in the best available population prevalence for us to label the medical condition tested for as potentially associated with SFPN. The cost of screening to identify one abnormal blood-test result was calculated as 100/(ABTR % $\times$ unit test cost). Since not all patients underwent all studied tests, this estimates the minimum cost of identifying one ABTR.

Results

Sample characteristics

Two hundred thirteen patients had objective confirmation of SFPN; 166 by skin biopsy (including all 6 with nerve biopsies diagnostic for SFPN), and 47 by AFT alone. Among them, 92 % (195) had one or more blood-test results available and thus were included in the study. Only 2.5 % had known current or prior diabetes, confirming that this was a valid sample of iiSFPN patients. Patients had been referred by 29 community and hospital-based physicians of various medical specialties. Their mean age was 43.0 $\pm$ 18.6 years (range 8–81 years), 70.3 % were female, and 94.9 % were Caucasian. Among the 41

Table 2 Prevalence of abnormal test results (ABTR) in the iiSFPN cohort and in comparator populations

Test (definition of abnormal result)	Medical condition tested for	Prevalence of ABTR in sample (*n*)	Population prevalence of ABTR and source of population data
ACE (high)	Sarcoidosis [24]	44.6% (83)	Not evaluated due to positive predictive value = 0
ESR (high)	Inflammation/infection [12, 43]	28.0% (157)	5.0% in Norway [70]
ANA (≥ 1:160)	Lupus/rheumatic disease [43]	27.5% (153)	8.9% in Brazil [21]
2-hr OGTT value for prediabetes (140-149 mg/dL)	Impaired glucose tolerance (prediabetes) [5]	25.0% (8)	44.9% in US adults 45-64y from A1C , FPG, or 2-hr OGTT value NHANES [40]
Fasting plasma glucose for prediabetes (100-125 mg/dl)	Impaired fasting plasma glucose (prediabetes) [5]	25.0% (20)	44.9% in US adults 45-64y from A1C, FPG, or 2-hr OGTT value NHANES [40]
Triglycerides (high)	Hypertriglyceridemia [28]	24.7% (97)	30% NHANES [66]
Complement C4 (low)	Inflammation/vasculitis [43]	15.7% (115)	10.4% WHS [31]
Liver AST/ALT (high)	Fatty liver, alcoholism, hepatitis [73]	14.8% (162)	10% NHANES [29]
A1C for prediabetes (≥ 5.7%, <6.5)	Recent hyperglycemia (prediabetes) [5]	14.7% (109)	44.9% in US adults 45-64y from A1C, FPG, or 2-hr OGTT value [40]
C-reactive protein (high)	Injury/inflammation [25]	12.6% (95)	7.1% WHS [30]
Complement C3 (low)	Autoimmunity/vasculitis [43]	11.0% (118)	2.7% WHS [31]
AntiRo/SS-A	Sjögren's syndrome [49, 56]	9.2% (98)	0.7% WHS [31], 3.9% NHANES [54]
AntiLa/SS-B	Sjögren's syndrome [49, 56]	9.2% (98)	1.2% WHS [31], 2.4% NHANES [54]
Lyme (IgG Western Blot)	Lyme disease [25]	8.7% (104)	No data found on immunoblot positivity
A1C for diabetes (≥ 6.5%)	Recent hyperglycemia/diabetes [60]	5.5% (109)	5.8% occult DM by A1C or OGTT age 45-64 NHANES [40]
Thyroid stimulating hormone (TSH) (high)	Hyperthyroidism [1]	4.1% (145)	0.5% NHANES [27]
SPEP/IFIX	Monoclonal gammopathy [74]	3.9% (128)	3.2% for age > 50y [35]
IgA TTG antibody (high)	Celiac sprue [9]	3.5% (109)	0.5-1.0% U.S. estimate [20]
Creatinine (high)	Renal disease, Fabry [67]	2.5% (162)	No data found
Thyroid stimulating hormone (TSH) (low)	Hypothyroidism [47]	2.1% (144)	0.3% NHANES [27]
Folate (low)	Folate deficiency [33]	2.0% (49)	0.1% [44]
Vitamin B12 (low)	Vitamin B12 deficiency [60]	1.5% (135)	3.8% [52]
Hepatitis C antibodies	Hepatitis C [10]	1.1% (88)	1.6% NHANES [4]
Fasting glucose for diabetes including OGTT (≥ 126 mg/dl)	Diabetes mellitus [5]	0.0% (20)	5.8% occult DM by A1C or OGTT age 45-64 NHANES [40]
2-hr value from OGTT for diabetes (≥ 200 mg/dL)	Diabetes mellitus [5]	0.0% (8)	5.8% occult DM by A1C or OGTT age 45-64 NHANES [40]

In the "Test" column, "high" indicates that only values above the reference range were labeled as abnormal and "low" indicates that only values below the reference range were labeled as abnormal

Green shading indicates tests in which the prevalence of an ABTR in the iiSFPN cohort was ≥ 300% than the population prevalence, thus meeting this study's criteria for excess prevalence and an association; yellow shading indicates tests in which the comparison yielded uncertain results because the prevalence of ABTR in the iiSFPN cohort was greater than the population prevalence by < 300%, red shading indicates tests in which an ABTR was more common in the population than in the iiSFPN cohort, and no shading indicates that this analysis was not conducted because of missing population data, small sample size, or no positive predictive value of the abnormal test result (for ACE)

A1C hemoglobin A1C, *ACE* angiotensin converting enzyme, *ANA* antinuclear antibodies, *ALT* alanine transaminase, *AST* aspartate aminotransferase, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *OGTT* 2 h oral glucose tolerance test, *IFIX* immunofixation, *SPEP* serum protein electrophoresis, *IgA antiTTG* immunoglobulin A antibodies to tissue transglutaminase

available results of EMG/NCS, 27 % identified concomitant large-fiber polyneuropathy. Regarding somatic symptoms, 86 % of the patients had chronic widespread pain and 87 % had other sensory symptoms. Regarding the studied symptoms of dysautonomia, 87 % had cardiovascular complaints, 72 % had chronic headache, 66 % had gastrointestinal symptoms, 47 % reported altered sweating, and 42 % had urological complaints.

Prevalence of abnormal blood-test results (ABTR)

Overall, 71 % of patients had ≥1 ABTR. The most common were high ACE in 44.6 %, high ESR in 28.0 %, and ANA ≥1:160 in 27.5 %. As shown in Table 2, the prevalence of abnormal test results diagnostic for diabetes ranged between 0.0 and 5.5 % for the three different blood tests analyzed. For prediabetes, between 15.0 and 25.0 % of patients had abnormalities on the tests used to identify this. Among patients with levels of complement C3 and C4, 18 had only low C4, 12 had only low C3, and both levels were low in 6. The only sex-related association was that hypertriglyceridemia was more prevalent in males ($p = 0.026$). Abnormal test results for creatinine ($p = 0.046$) and ESR ($p = 0.029$) were more common in older (above median age) than younger subjects. There were too few non-Caucasians to detect race effects.

Specificity of abnormal blood-test results

Table 2 summarizes the best available data about population prevalence of each ABTR. Abnormal results of all six tests for diabetes and prediabetes were less prevalent in the iiSFPN cohort than in the NHANES-surveyed US population, which reported 5.8 % prevalence of undiagnosed diabetes and 44.9 % total prevalence of prediabetes among US adults age 45–64 [45]. Occult diabetes and prediabetes were therefore far less common among studied iiSFPN patients than in the population.

In contrast, none among the eight blood-test markers of autoimmunity, immune dysregulation, and inflammation (high ESR, ANA ≥1:160, C-reactive protein, low C3, low C4, presence of anti-Ro/SS-A, anti-La/SS-B, IgA-anti-TTG) had ABTR prevalences below comparator population prevalences (Table 2). The prevalences of high ESR, high ANA, and autoantibodies diagnostic of Sjögren's and celiac were at least 300 % of comparator population prevalences, meeting this study's definition of a potentially significant association. The cohort's 27.5 % prevalence of ANA ≥1:160 exceeds the comparator 8.9 % Brazilian population prevalence of ANA ≥1:160 [46] as well as the 13.8 % US population prevalence for titer ≥1:80 [47]. The excess prevalences of both low and high TSH suggest associations not only with hypothyroidism but also with thyroiditis, which is often autoimmune [48]. Together, these findings suggest that occult dysimmune/inflammatory conditions may contribute to iiSFPN in this environment.

Since we did not find the population prevalence of high ACE, the specificity of the 45 % measured prevalence of high ACE was evaluated by investigating how many patients with high ACE actually had sarcoidosis. Twenty nine iiSFPN patients with high ACE had been further specifically evaluated for sarcoidosis, with chest CT performed in 7. None among the 29 was found to have sarcoidosis, so high ACE had zero positive predictive value or evidence of specificity in the current context.

Cost effectiveness of abnormal blood-test results

As shown in Table 3, the Medicare reimbursement for each blood test ranged from $3.69 for ESR to $24.46 for Sjögren's autoantibodies. The total per-patient reimbursement for all tests was $290.63. The reimbursement for each individual test varied by less than 10-fold. But when the frequency of ABTR was factored in the cost of screening enough patients to obtain one abnormal test result ranged between $13.17 for ESR to $1441.82 for hepatitis C, a 100-fold difference.

Discussion

This study evaluated the sensitivity and cost of recommended screening tests for occult causes of iiSFPN in the northeastern US. It also considered the possibility that individual medical conditions tested for might be specifically associated with iiSFPN. This is the largest sample of patients with small-fiber axonopathy (Table 1) and one of the first to consider the costs of these blood tests. It has the limitations of retrospective studies including incomplete data. The fact that this was a single-center study conveys risk of referral bias. To reduce this, patients were not required to have been evaluated by any MGH physician, and the sample comprised patients referred for neuropathy testing by 29 physicians from diverse specialties practicing in the community and at other hospitals as well as at MGH. We also reduced referral bias by including patients who had undergone all available recommended diagnostic tests for SFPN rather than just one test. One limitation is that the demographics of the study sample did not precisely match the demographics of comparator epidemiologic surveys, meaning that the analyses about the specificity of these ABTR are imprecise. This is unavoidable in studies that use population-based controls, but the other option, case–control studies, can also be inaccurate due to much smaller samples. To compensate for this uncertainty, we used a very conservative approach of only reporting medical

Table 3 Medicare reimbursement rate for blood tests for occult causes of initially idiopathic SFPN (iiSFPN)

Blood test	More prevalent in iiSFPN	Cost per one test	Screening cost per one ABTR
ESR	YES	$3.69	$13.17
ANA	YES	$16.49	$59.96
C3	YES	$16.38	$148.91
Sjögren's antibodies (SS-A/SS-B)	YES	$24.46	$265.87
IgA antiTTG	YES	$15.62	$446.29
TSH (high or low)	YES	$22.93	$477.71
Folate	YES	$20.06	$1,003.00
Liver enzymes AST/ALT	PERHAPS	$7.06	$47.70
C-Reactive protein	PERHAPS	$7.06	$56.03
C4	PERHAPS	$16.38	$104.33
SPEP/IFIX	PERHAPS	$5.00	$128.21
Fasting glucose to detect prediabetes	NO	$5.36	$21.44
Triglycerides	NO	$7.84	$31.74
ACE	NO	$19.92	$44.66
OGTT to detect prediabetes	NO	$17.56	$70.24
A1C to detect prediabetes	NO	$13.24	$90.07
A1C to detect diabetes	NO	$13.24	$240.73
Vitamin B12	NO	$20.41	$1,360.67
Hepatitis C antibodies	NO	$15.86	$1,441.82
Lyme (Western blot)	unknown	$19.49	$224.02
Creatinine	unknown	$6.99	$279.60

Blood tests are grouped by their level of association with iiSFPN, and within those groups by screening cost per one ABTR. Fasting glucose and 2-hour OGTT to detect diabetes are not included because no patients had abnormal results thus screening costs would be infinite

conditions tested for as potentially associated with iiSFPN when prevalences of ABTR were at least three times higher in the iiSFPN cohort than in the reference population. Such large differences are unlikely to be caused merely by mismatches between the iiSFPN sample and population controls. To further compensate for potential referral bias, we also included in our specificity considerations the prevalences of individual ABTRs reported from all other available studies, as discussed below. When multiple independent investigators all reported similar ABTR prevalences, and when these all aligned either below or above population prevalences, it added weight to our impressions about possible occult medical contributors to iiSFPN. In so far as we know, this is the first such study to factor results from other cohorts into its conclusions. Another limitation is that MGH's electronic record only rarely specified if glucose measurements were 2-h values from OGTT. Since we could definitively identify only eight 2-h values, we did not include 2-h values in the specificity analyses. In addition, no population data were identified with which to evaluate specificity of the sample's prevalences of high creatinine or Lyme seropositivity.

Despite the fact that diabetes is the largest cause of SFPN in the US and in most other developed countries, the contribution of occult diabetes and prediabetes to iiSFPN remains uncertain. The 2011–2012 NHANES data indicate that the US prevalence of diabetes in adults between 45 and 65 years was 17.5 %, of which 5.8 % was undiagnosed/occult [45]. In contrast, the MGH iiSFPN cohort had a smaller 5.5 % prevalence of diabetes by A1c (Table 2) of which 2.5 % was known. Two other idiopathic neuropathy cohorts had higher rates of undiagnosed diabetes, e.g., 13 % in Utah [28] and 9.2 % in New York [5], but two others were similar, 1.7 % in Michigan [9], and 3 % in New York [49], so the overall importance of undiagnosed diabetes as a contributor to initially idiopathic SFPN remains uncertain. These prevalence differences might reflect local or demographic differences or different care patterns, so decisions on whether and how to test for undiagnosed diabetes should be made locally.

The evidence is stronger that occult prediabetes is not overrepresented among patients with initially idiopathic sensory neuropathies [50, 51]. Its prevalence here (14.7 %) and in all other US neuropathy cohorts (6.1 and 22.7 % in Michigan [6, 9], 11 % in Ohio [52], 7 and 11 % in New York [5, 49]) are far below the NHANES-based US population prevalences (e.g., 44.9 % for adults aged 45–65) [45]. A prospective Minnesota study that found no increased risk for sensory polyneuropathy among prediabetic patients versus healthy controls also supports the lack of an association [53]. The situation appears similar for hypertriglyceridemia. Although it increases the risk of diabetics developing polyneuropathy [54], prevalences in iiSFPN cohorts (24 % here, 34 % in Ohio [55]) do not exceed the 33 % population prevalence [56].

Autoimmune neuropathies are divided into those associated with systemic or multi-organ autoimmunity, and nerve-specific conditions. Systemic lupus erythematosus [36], Sjögren's [35, 57], and celiac [37–39, 58, 59] are systemic or multi-organ autoimmune conditions that are thought to include SFPN, although odds ratios have not been determined. Serologic markers for all three conditions were far more often abnormal in the MGH cohort than in the population (Table 2), further evidence linking these conditions to SFPN and suggesting that some cases of iiSFPN are immune mediated. The current study reported the highest prevalence of ANA $\geq$1:160 (27.5 %), with other surveys reporting 11 % [55], 12.6 % [6], and 3 % [28]. Similarly, the 9.8 % prevalence of SS autoantibodies here exceeds the 1.8 % reported from New York [5] and the 7.5 % prevalence of SS (test unspecified) from Milan [11]. The high prevalences at MGH presumably reflect this cohort's relative youth and female predominance as compared to other neuropathy cohorts. Of note, fewer than half of patients with SS-associated painful neuropathy are SS seropositive [57], thus the actual prevalence of Sjögren's syndrome is even higher. However, the 28 % prevalence of high ESR here is comparable to the 22.3 % prevalence identified in an older, male-predominant Michigan cohort [6].

There are well-known large-fiber-specific autoimmune neuropathies affecting myelinating Schwann cells or nodes of Ranvier including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor mononeuropathy. Autoimmune small-fiber-predominant ganglionopathies/neuronopathies are also recognized, particularly in patients with SS or cancer [60]. It is logical that small-fiber-predominant autoimmune axonopathies should also exist, and we and others have reported cases, although these conditions are not yet well-characterized [15, 61–63]. Dysimmunity may be a more common cause of neuropathy in children and young adults, since they lack most other risks [15, 62]. The slightly elevated prevalence of complement consumption seen here might signal involvement of autoantibodies, which contribute to other neuropathies in young cohorts. Other surveys did not measure complement (Table 1), but our group reported complement consumption among young patients with iiSFPN [15].

There is an established association between monoclonal gammopathies and large-fiber demyelinating polyneuropathy, but the question of an association with SFPN has not yet been examined. The 3.9 % sample prevalence of monoclonal gammopathy here and rates from most other US neuropathy studies (3.0 % in Utah [28], 4.0 % in Michigan [6], and 7.0 % in New York [5]) are slightly higher than the 3.2 % prevalence of MGUS in US adults over age 50, even though they include patients under 50 [64]. Although inconclusive, this comparison suggests a potential association. The same situation applies to elevated liver enzymes, a marker for alcoholism and hepatitis.

Regarding nutritional contributors, folate deficiency usually produces large-fiber-predominant non-demyelinating sensory axonopathy [27] and folate levels do not correlate with risk of POTS, which is a common symptom of SFPN [65]. Given the lack of evidence for an association here, plus the rarity of folate deficiency in other US neuropathy cohorts (0 %) [28] and the resulting high cost of screening (Table 2), it may not be cost-effective to screen for folate deficiency in iiSFPN in the northeastern US (Table 2). When vitamin B12 is considered, the 1.5 % prevalence of B12 deficiency here, and the 1.4 % prevalence in another New York study [5] and 2 % prevalence in Utah [28] are below population prevalence. We identified only one exception, the 6 % prevalence reported from one New York study [49]. Both low and high TSH were overrepresented in the MGH study sample by an order of magnitude as compared to population prevalence. The American Academy of Neurology and other groups do not

recommend screening neuropathy patients for hypothyroidism [6, 8], but the elevated prevalence of abnormal test results in multiple studies, the intermediate cost of TSH screening, and the immediate actionability of abnormal results, suggest that TSH be considered for inclusion in screening recommendations for the US.

We also analyzed the costs of screening (Table 3). Medicare reimbursement for the three tests recommended by the AAN [8] (glucose, B12, and SPEP/IFIX) was $42.97/person, and ≥6.8 % of the MGH cohort would have at least one ABTR. The Utah group recommended screening panel (OGTT, B12, SPEP/IFIX, and ANA) [28] incurred Medicare costs of $59.46 per patient with ≥28.6 % probability of ≥1 abnormal result in the MGH cohort. In contrast, reimbursement for the two most cost-effective and specifically SFPN-associated blood tests from the current analysis—ESR and ANA—was only $20.18/person, and these two tests alone would convey a higher 38.5 % probability of detecting at least one abnormal test result in the MGH cohort, improving sensitivity plus reducing per-patient cost. Reimbursement for the three most cost-effective and specifically associated blood tests from the current analysis—ESR, ANA, and C3—was $36.56/person with 41.0 % probability of detecting one ABTR in MGH cohort. Reimbursement for the six most cost-effective and specifically associated blood tests from the current analysis—ESR, ANA, C3, Sjögren's autoantibodies, celiac testing (IgA-anti-TTG), and TSH—was $99.57/person with 45.6 % probability of detecting one ABTR in the MGH cohort.

Another consideration pertinent to cost effectiveness is the "actionability" of each ABTR [9]. Some tests, e.g., for diabetes, malnutrition, or infectious diseases are highly actionable since they reliably diagnose curable medical conditions. The actionability of dysimmune/inflammatory markers varies. The IgA anti-TTG test for celiac has >95 % sensitivity and specificity for detecting celiac, even for the many patients with "silent celiac" who lack gastrointestinal symptoms [66], and gluten-free diets reduce celiac-induced damage and symptoms. Thus, celiac tests may be more useful than the cheaper but less-actionable ANA and ESR. However, persistently elevated ANA or ESR typically prompt additional evaluation that can uncover treatable diagnoses, including systemic lupus erythematosus. And new treatments, e.g., for hepatitis C, add new rationale for screening. In accountable-care models, it may be most cost-effective to sequentially screen iiSFPN patients beginning with high yield, specific, low cost, actionable tests and performing others later only if needed. Testing decisions should also be personalized, since risks vary with patients' locations, demographic, personal, and family histories. Familial amyloid polyneuropathy is more prevalent in specific European regions for instance. Table 1 reveals that no prior studies reported the prevalences of abnormal results for every test they studied. Most did not include their study's definitions of normal and abnormal results for each test. More comprehensive reporting in future studies is encouraged to enable systematic review and pooling of results from multiple studies. This add power and can inform about even rare causes of initially idiopathic polyneuropathy.

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Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standards This retrospective study was approved by the Massachusetts General Hospital (MGH) institutional review board, which waived need for consent. The authors hereby declare that the research documented in the submitted manuscript has been carried out in accordance with the ethical standards.

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APPENDIX 7. Blood tests routinely applied to Veterans and Matched Controls for this study

Comprehensive Metabolic Panel
- SODIUM
- POTASSIUM
- CHLORIDE
- CO2
- BUN
- CREATININE
- GLUCOSE
- ALBUMIN
- TOTAL PROTEIN
- CALCIUM
- ALKALINE PHOSPHATASE
- TOTAL BILIRUBIN
- AST
- ALT
- GLOBULIN
- EGFR
- ANION GAP

Lyme IgG/IgM AB
HCV Antibody (Hep C)
Antinuclear antibody (ANA)
Complement C3
Complement C4
TSH
Vitamin B12
ESR
A1C
SPEP
Celiac
SS-A/Ro
SS-B/La
TTG IgG AB
TTG IgA AB
DSDNA AB

CBC and differential
- WBC
- RBC
- HGB
- HCT
- PLT
- MCV
- MCH
- MCHC
- RDW
- MPV
- NRBC
- ABSOLUTE NRBC
- DIFF METHOD
- NEUTS
- LYMPHS
- MONOS
- EOS
- BASOS
- % IMMATURE GRANS
- ABSOLUTE NEUTS
- ABSOLUTE LYMPHS
- ABSOLUTE MONOS
- ABSOLUTE EOS
- ABSOLUTE BASOS
- ABS IMMATURE GRANS

APPENDIX 8. Quad Chart

Characterizing Treatable Causes of Small-Fiber Polyneuropathy in Gulf War Veterans

GW130109
W81XWH-14-1-0499

PI: Anne Louise Oaklander, MD PhD **Org:** Massachusetts General Hospital **Award Amount:** $1,031,355

Study/Product Aim(s)

- **Aim I:** To develop a working Case Definition of SFPN, to objectively diagnose the presence or absence of SFPN among Gulf War veteran using validated anatomical and physiological diagnostic tests
- **Aim II:** To perform blood and skin-biopsy tests for the specific treatable causes of SFPN, compare the prevalence of identified causes in Gulf War veterans with or without SFPN

Approach

Task 1. Retrospective analysis and application of Delphi method to develop a Case Definition.
Task 2. Apply validated tests to veterans and diagnose SFPN (and controls).
Task 3. Identify treatable causes of SFPN in Gulf War veterans.

Accomplishments: Refined Case Definition and developed database of cases with which to test the Definition. Pictured are diagnostics for SFPN: autonomic function test, list of diagnostic blood tests, biopsy punch, skin biopsy slides

Timeline and Cost

Activities CY	14	15	16	17	18
Task 1.					
Task 2.					
Task 3.					
Estimated Budget ($K)	**$57K**	**$344K**	**$344K**	**$287K**	**$0K***

* No Cost Extension

Updated: 29 December 2018

Goals/Milestones
CY14 Goal – Project initiation
☑ IRB and HRPO protocol approval
CY15 Goals – Begin Delphi process, identify best tests
☑ Retrospective study of relevant blood tests
☑ Engage Global panel of experts to define SFPN diagnostics
CY16 – CY17 Goals – Case definition of SFPN
☑ Develop database of cases
☑ Apply Delphi method, experts validate
CY17 – CY18 Goals – Human studies
☑ Collect detailed medical histories
☑ Recruitment, apply validated tests per Case Definition
Comments/Challenges/Issues/Concerns
- Slow responses of Global experts, delayed subject recruitment
- Project extended at no-cost

Budget Expenditure to Date
Project complete