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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 (SFPN). 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 first year of this study, an Internet-based framework for developing a formal Case Definition of SFPN was developed. Global experts were invited to participate in a Delphi method process to determine the most reliable markers for SFPN (Case Definition). We also will determine if common blood tests have utility in diagnosing SFPN because some causes are treatable. We performed a preliminary retrospective study to identify blood tests with historically good predictive value.

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

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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 show that among 38 Gulf War veterans and 41 matched controls, 49% of veterans had objective evidence of SFPN vs. 12% of controls [3]. However, interpretation is uncertain as there is no case definition of SFPN. We propose to recruit a group of global experts and use validated methods to develop a case definition of SFPN. We will then apply this case definition in combination with clinical tests to not only look for the prevalence of SFPN among Gulf War veterans, but also to look for potentially treatable causes.

KEYWORDS:

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

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, only Task 1 under Specific Aim I was to be accomplished largely in the first year of this study (up to month 14):

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.

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 that serves as the entry point to a secure platform where the global panel of Experts can upload actual de-identified case reports 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 recruited National and International experts to develop the Case Definition. They currently include:

National:

Professor Didier Cros, MD (Massachusetts General Hospital, Boston, MA)

Professor Roy Freeman, MD (Beth Israel Deaconess Medical Center, Boston, MA)

Professor David Herrmann, MD (University of Rochester, Rochester, NY)

Professor Norman Latov, MD, PhD (Weill Cornell Medical College, New York, NY)

Professor Adam Loavenbruck, MD (Mayo Clinic, University of Minnesota, Rochester, MN)

Professor Glenn Lopate, MD (Washington University in St. Louis, MO)

International:

Professor Colin Chalk, MD, CM, FRCPC (McGill University, Montreal, Canada)

Professor Catharina Faber, MD, PhD (Maastricht University Medical Centre, Maastricht, Netherlands)

Professor Alejandra Gonzáles-Duarte, MD (Instituto Nacional de Ciencias Médicas y Nutrició Salvador Zubiran, Tlalpa, Mexico)

Professor Riadh Gouider, MD (Razi Hospital, University of Medicine of Tunis, La Manouba, Tunisia)

Professor Sung-Tsang Hsieh, MD, PhD, MPH (National Taiwan University Hospital, Taipei, Taiwan)

Professor Thierry Kuntzer, MD (Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland)

Professor Giuseppe Lauria, MD (Instituto Carlo Besta, Milan, Italy)

Professor Jean-Pascal Lefaucheur, MD, PhD (Hôpital Henri-Mondor, Public Hospitals of Paris, Paris-Est Créteil University, Créteil, France)

Professor Manoj Menezes, MD (University of Sydney, Children's Hospital, Westmead, Australia)

Professor Osvaldo Nascimento, MD (Universidade Federal Fluminense, Copacabana, Rio de Janeiro, Brazil)

Professor Claudia Sommer, MD (University of Würzburg, Würzburg, Germany)

Professor Judith Spies, MBBS, FRACP, PhD (University of Sydney, Camperdown, Australia)

Professor Thirugnanam Umapathi, MBBS, MRCPE, FAMS (Neurology) (National Neuroscience Institute, Singapore)

Professor Isin Unal Cevik, MD, PhD (Hacettepe University Faculty of Medicine, Sihhiye- Ankara, Turkey)

We plan to invite additional experts from the US, Israel, Japan, Africa, South America, and the UK.

Additionally, we have assigned another group of leaders to a Scientific Advisory Board to steer the Delphi process. They currently include:

Scientific Advisory Board:

Professor Verne S. Caviness, Jr., MD, DPhil (Massachusetts General Hospital and Harvard Medical School, Boston, MA)

Professor Alain Créange, MD, PhD (Hôpital Henri Mondor, Paris Est Créteil, France)

Professor John England, MD (Louisiana State University School of Medicine, New Orleans, Louisiana)

Professor Eva Feldman, MD, PhD (University of Michigan Health System, Ann Arbor, Michigan)

Professor Riadh Gouider, MD (Razi Hospital, Tunis, Tunisia)

Professor Mary M. Reilly, MD, FRCP, FRCPI (University College London, England)

4. We hosted an International videoconference between the MGH-based Nerve Unit (Oaklander Lab) and the France-based collaborative team at the Henri Mondor Hospital (Prs. Créange and Lefaucheur). In addition to being an invited expert on neuropathy, Professor Créange is an authority on the Delphi method.

5. To advance Task 2 (Apply validated tests to veterans and diagnose SFPN) we met with Drs. Jorge Serrador and Drew Helmer of the East Orange, NJ VA Hospital and War-Related Injury and Illness Study Center (WRIISC) to develop strategies for recruiting Gulf War Veterans.

Aim II:

While awaiting completion of the secure portion of the collaborative website for developing the Case Definition, we performed preliminary retrospective studies under Aim II to identify the blood tests that may have the best predictive value for SFPN:

1. 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 21commonly available blood tests reported in the literature as useful for identifying causes of SFPN (Table 1) [4,5,6]. 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 [7].

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

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 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.

We presented posters on these preliminary results at the 2015 Meeting of the Peripheral Nerve Society (PNS) [8] and the 2015 Meeting of the American Neurological Association (ANA) [9]. The posters are included as Appendices 1 and 2, respectively.

The future plan under this grant is to refine the list of blood tests and apply the ones with most utility to Gulf War Veterans who are additionally well-characterized by history, skin biopsy,

dermatopathology, and autonomic function testing, and to age-matched controls to look for the prevalence of markers of SFPN that are indicative of causality.

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

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

How were the results disseminated to communities of interest?

This project so far has developed an Internet framework to increase awareness within the affected community and 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 also presented preliminary results under Aim II at two scientific meetings (Peripheral Nerve Society and the American Neurological Association) as described above.

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

During the next reporting period, we plan to engage the global experts to arrive at a consensus Case Definition of small-fiber polyneuropathy (SFPN) via the Delphi method. This will allow us to more accurately identify verified SFPN among the research volunteers whom we will recruit in the coming year, to include Gulf War Veterans of diverse health histories and normal control volunteers.

IMPACT:

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

A goal of this project is to generate a formal Case Definition for small-fiber polyneuropathy which is intended to guide future practice of diagnosticians. Toward that goal, we have initiated creating a website with public and private Internet pages, to raise awareness of SFPN among the general population and health care professionals through the public pages, and to allow global experts to access the private (secure) pages to add case reports to arrive at a consensus 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.

CHANGES/PROBLEMS:

Changes in approach and reasons for change

There have been no changes in our approach, nor are any changes anticipated. We performed a preliminary study related to Aim II ahead of sequence as the development of the collaboration website took slightly longer than anticipated.

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

The initial step of creating the private portion of the Internet site which is tied to the secure data collection tool REDCap was delayed as Kate O'Neil took a leave of absence. However, we then accelerated the remainder of the website by engaging the bioinformatics team of the Department of Neurology to design the public portion and to begin adding the private portion. We also proceeded to accomplish a portion of studies related to Aim II ahead of schedule.

Changes that had a significant impact on expenditures

We delayed recruiting study subjects because of the delay in arriving at the expert consensus Case Definition. However, the majority of recruitment is scheduled beyond the first year.

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.

PRODUCTS:

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 is under development and is part of an overall laboratory website that describes small-fiber polyneuropathy, associated research, and resources. It will also serve as an effective recruiting tool for Veterans and patients. The site can be accessed at http://NeuropathyCommons.org .

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 design of the collaboration website and provided content to the website, identified and invited the International collaborators to participate in developing the case definition, and contributed the analysis of relevant blood tests for neuropathy.
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 obtained IRB and HRPO approval for this project and maintained IRB compliance. He also provided content to the collaboration website, arranged videoconferences with the global network of experts, discussed the case definition development with the experts, and advised on the Delphi Method.
Funding Support:	No other funding support was used to conduct the work under this award.

Name:	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 assisted with maintaining IRB (and HRPO) documentation, contributed content to the collaborative website, and advised on the design of the secure portion of the collaborative website in accordance with the Delphi Method.
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, and processed administrative activities related to this study.
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.

SPECIAL REPORTING REQUIREMENTS

None.

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ACRONYMS AND ABBREVIATIONS

ACE Angiotensin converting enzyme
AFT Autonomic function test
ANA Antinuclear antibody
AST/ALT aspartate transaminase/ alanine transaminase
C, C3, C4 Complement components
CMI Chronic multisymptom illness
CWP Chronic widespread pain
DOD Department of Defense
ESR Erythrocyte sedimentation rate
GTT Glucose tolerance test
Hgb Hemoglobin
HRPO Human Research Protection Office
IgA Immunoglobulin A
IRB Institutional review board
MGH Massachusetts General Hospital
PI Principal Investigator
REDCap The Research Electronic Data Capture platform
SFPN Small-fiber polyneuropathy
SPEP/IFIX serum protein electrophoresis and immunofixation
SS-A, SS-B Sjögren's-syndrome-related antigens A, B
TTG Tissue Transglutaminase Antibodies

APPENDIX 1. 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)

Magdalena Lang MD[1], Roi Treister PhD[1], Anne Louise Oaklander MD PhD[1,2]

[1] Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, 02114, USA

[2] Department of Pathology (Neuropathology), Massachusetts General Hospital, Boston, MA, 02114, USA

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

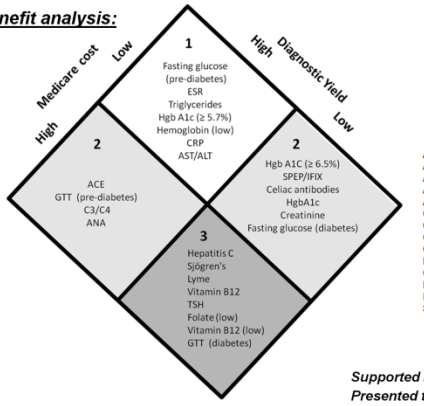
- **Review of 415 records yielded 195 qualifying patients referred by 29 physicians.**
- **Patients were 70% female, 95% Caucasian, mean age 43.0 ± 18.6 years; 147 had SFPN confirmed by skin biopsy, 42 by AFT and 6 by nerve biopsies.**
- **Overall, 57% of patients had ≥ 1 abnormal blood-test result, 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% (182)	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 2. 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	$36.03
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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