

# Small Fiber Neuropathy in Veterans With Gulf War Illness

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**Background:** Gulf War veterans deployed to operations Desert Shield and Desert Storm returned with chronic multisystemic symptoms. This Gulf War Illness (GWI) has defied attempts to identify an underlying etiology. Pain and other symptoms attributable to autonomic nervous system (ANS) dysfunction are common, which may suggest a pathophysiologic underpinning. Small fiber neuropathy (SFN) presents with similar symptoms. Toxic exposures have been implicated in both SFN and GWI.

**Methods:** A retrospective chart review of clinical data at the New Jersey War Related Illness and Injury Study Center addressed the following questions: (1) how common was biopsy-confirmed SFN in veterans with GWI; (2) do veterans with GWI and SFN report more symptoms attributable to ANS dysfunction as compared to veterans with GWI and no SFN; and (3) can SFN in veterans with GWI and SFN be explained by conditions commonly associated with SFN? Chart review abstracted GWI status, skin biopsy results, and ANS symptom burden. For veterans with GWI and SFN, additional chart abstraction was explored for commonly reported contributing conditions.

**Results:** From March 1, 2015, to January 31, 2019, 51 Gulf War veterans evaluated at the War Related Illness and Injury Study center had a skin biopsy. Of these, 42 (83%) were diagnosed with GWI and 24 of 42 (57%) also had SFN. No differences were observed in ANS symptoms when compared with veterans with GWI and no SFN. A potential etiology for SFN was identified in 16 of 24 (67%) veterans with GWI and SFN, increasing to 19 (79%) when hyperlipidemia was included. Our analysis did not identify an explanation in 5 of 24 (21%) veterans with GWI and SFN.

**Conclusions:** SFN was common in this clinical sample of veterans diagnosed with GWI. A well-established potential etiology was identified in most cases of SFN. About 20% of veterans with GWI in our clinical sample had idiopathic SFN, and it is plausible that deployment-related exposures could have contributed to this condition. Symptoms of ANS are prevalent in GWI, though SFN cannot solely account for this. Our study does not generally support SFN as etiologic for GWI, though this may still be relevant for some. Additional research is required to explore relationships between Gulf War exposures and SFN.

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*Fed Pract.* 2024;41(5).  
Published online May 15.  
doi:10.12788/tp.0470

Following deployment to operations Desert Shield and Desert Storm (Gulf War) in 1990 and 1991, many Gulf War veterans (GWWs) developed chronic, complex symptoms, including pain, dyscognition, and fatigue, with gastrointestinal, skin, and respiratory manifestations. This Gulf War Illness (GWI) is reported to affect about 30% of those deployed. More than 30 years later, there is no consensus as to the etiology of GWI, although some deployment-related exposures have been implicated.<sup>1</sup>

Accepted research definitions for GWI include the Centers for Disease Control and Prevention and Kansas definitions.<sup>2</sup> The US Department of Veterans Affairs (VA) uses the terminology *chronic multisymptom illness* (CMI), which is an overarching diagnosis under which GWI falls. Although there is no consensus case definition for CMI, there is overlap with conditions such as fibromyalgia, myalgic encephalomyelitis/chronic fatigue syndrome, and irritable bowel syndrome; the VA considers these as qualifying clinical diagnoses.<sup>3</sup> The pathophysiology of GWI is also unknown, though a frequently reported unifying feature is that of autonomic nervous system (ANS) dysfunction. Studies

have demonstrated differences between veterans with GWI and those without GWI in both the reporting of symptoms attributable to ANS dysfunction and in physiologic evaluations of the ANS.<sup>4-10</sup>

Small fiber neuropathy (SFN), a condition with damage to the A- $\delta$  and C small nerve fibers, has been proposed as a potential mechanism for the pain and ANS dysfunction experienced in GWI.<sup>11-13</sup> Symptoms of SFN are similar to those of GWI, with pain and ANS symptoms commonly reported.<sup>14,15</sup> There are multiple diagnostic criteria for SFN, the most commonly used requiring the presence of appropriate symptoms in the absence of large fiber neuropathy and a skin biopsy demonstrating reduced intraepidermal nerve fiber density.<sup>16-19</sup> Several conditions reportedly cause SFN, most notably diabetes/prediabetes, autoimmune disease, vitamin B12 deficiency, monoclonal gammopathies, celiac disease, paraneoplastic syndromes, and sodium channel gene mutations.<sup>20</sup> Hyperlipidemia has been identified as a contributor, although it has been variably reported.<sup>21,22</sup>

Idiopathic neuropathies, SFN included, may be secondary to neurotoxicant exposures.

Agents whose exposure or consumption have been associated with SFN include alcohol most prominently, but also the organic solvent n-hexane, heavy metals, and excess vitamin B<sub>6</sub>.<sup>20,23-25</sup> Agents associated with large fiber neuropathy may also have relevance for SFN, as small fibers have been likened to the “canary in the coal mine” in that they may be more susceptible to neurotoxicants and are affected earlier in the disease process.<sup>26</sup> In this way, SFN may be the harbinger of large fiber neuropathy in some cases. Of specific relevance for GWVs, organophosphates and carbamates are known to produce a delayed onset large fiber neuropathy.<sup>27-30</sup> Exposure to petrochemical solvents has also been associated with large fiber neuropathies.<sup>31,32</sup>

The War Related Illness and Injury Study Center (WRIISC) is a clinical, research, and education center established by Congress in 2001. Its primary focus is on military exposures and postdeployment health of veterans. It is located at 3 sites: East Orange, New Jersey; Washington, DC; and Palo Alto, California. The New Jersey WRIISC began a program to evaluate GWVs with characteristic symptoms for possible SFN with use of a skin biopsy.

We hypothesized that SFN may underly much of GWI symptomatology and may not be accounted for by the putative etiologies detailed in review of the medical literature. This retrospective review of clinical evaluations for SFN in GWVs who sought care at the New Jersey WRIISC explored and addressed the following questions: (1) how common is biopsy-confirmed SFN in veterans with GWI; (2) do veterans with GWI and SFN report more symptoms attributable to ANS dysfunction when compared with veterans with GWI and no SFN; and (3) can SFN in veterans with GWI and SFN be explained by conditions and substances commonly associated with SFN? Institutional review board approval and waiver of consent was obtained from the Veterans Affairs New Jersey Health Care Center for the study.

## METHODS

A retrospective chart review was conducted on veterans evaluated at the WRIISC from March 1, 2015, to January 31, 2019. Inclusion criteria were: deployment to operations Desert Shield and Desert Storm between August 2, 1990, and February 28,

**TABLE 1** Gulf War Veterans With WRIISC Comprehensive Postdeployment Evaluation Skin Biopsy, 2015 to 2019 (N = 51)

Characteristics	Results
Sex, No. (%)	
Male	49 (96)
Female	2 (4)
Age, mean (SD), y	48.6 (3.7)
Military branch, No. (%)	
Army	23 (45)
Marine Corps	11 (22)
Multiple/unspecified	5 (10)
Navy	4 (8)
Air Force	3 (6)
Army Reserve/Guard	3 (6)
Marine Corps Reserve	1 (2)
Air National Guard	1 (2)
Gulf War Illness diagnosis, No. (%)	
Positive	42 (82)
Negative	9 (18)
Small fiber neuropathy diagnosis, No. (%)	
Positive	28 (55)
Gulf War Illness positive	24 (47)
Gulf War Illness negative	4 (8)
Negative	23 (45)

Abbreviation: WRIISC, War Related Illness and Injury Study Center.

1991, and skin biopsy conducted at the WRIISC. Skin biopsies were obtained at the discretion of an examining clinician based on clinical indications, including neuropathic pain, ANS symptoms, and/or a fibromyalgia/chronic pain-type presentation.

Electronic health record review explicitly abstracted GWI status, results of the skin biopsy, and ANS symptom burden as determined by the Composite Autonomic Symptom Scale 31 (COMPASS 31) completed at the time of the WRIISC evaluation. Determination of GWI was established as per the clinical opinion of the WRIISC lead clinician or environmental exposure clinician as evidenced by a diagnosis of fibromyalgia or chronic fatigue syndrome, or explicit statement of CMI/GWI in the patient assessment. A diagnosis of SFN was established if clinical signs were present and an intraepidermal nerve fiber density below the lower limits, as compared to normative data from the clinical diagnostic laboratory (Therapath Neuropathology), was documented.

COMPASS 31 assesses symptoms across 6 domains (orthostatic, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor). Patients are asked about

**TABLE 2** COMPASS 31 Scores in Veterans With Gulf War Illness

Scale domains	Small fiber neuropathy, mean (SD)		P value
	Positive (n = 18)	Negative (n = 17)	
Orthostatic	4.3 (2.2)	4.4 (2.5)	.98
Vasomotor	1.1 (1.7)	1.2 (1.8)	.83
Secretomotor	2.3 (1.7)	2.5 (1.8)	.74
Gastrointestinal	12.8 (4.5)	11.8 (5.3)	.55
Bladder	1.1 (1.2)	0.8 (1.2)	.41
Pupillomotor	7.6 (4.1)	8.1 (3.9)	.74
Total, weighted	38.3 (14.3)	37.8 (18.9)	.93

Abbreviation: COMPASS 31, Composite Autonomic Symptom Scale 31.

**TABLE 3** Explanations for Small Fiber Neuropathy in Gulf War Illness (n = 24)

Etiologies <sup>a</sup>	No. (%)
Prediabetes/diabetes	11 (46)
Medication	5 (21)
Alcohol abuse within 5 y	2 (8)
Autoimmune condition	1 (4)
Monoclonal gammopathy	1 (4)
Vitamin B <sub>6</sub> toxicity, > 50 ug/L	1 (4)
≥ 1 condition	16 (67)
Medically unexplained	5 (21)

<sup>a</sup>Hyperlipidemia has been reported as contributing to small fiber neuropathy and was identified in 14 (58%) individuals; when hyperlipidemia is included, 19 (79%) skin biopsy-confirmed cases of small fiber neuropathy in veterans with Gulf War Illness could potentially be explained but 5 (21%) were considered idiopathic.

symptom frequency (rarely to almost always), severity (mild to severe), and improvement (much worse to completely gone). Individual domain scores and a total weighted score (0-100) have demonstrated good validity, reliability, and consistency in SFN.<sup>33,34</sup>

In veterans with GWI and documented SFN, a health record review was performed to identify potential etiologies for SFN (Appendix).

### Statistical Analysis

Microsoft Excel and IBM SPSS 12.0.1 for Windows were used for data collection and statistical analysis. Fisher exact test was used for comparing the prevalence of SFN in veterans with GWI vs without GWI. The

independent samples *t* test was used for comparing COMPASS 31 scores for veterans with GWI by SFN status.  $\alpha < .05$  was used for determining statistical significance. For those GWVs documented with SFN and GWI, potential explanations were documented in total and by condition.

## RESULTS

From March 1, 2015, to January 31, 2019, 141 GWVs received a comprehensive in-person clinical evaluation at the WRIISC and 51 veterans (36%) received a skin biopsy and were included in this retrospective observational study (Figure). The mean age was 48.6 years, and the majority were male and served in the US Army. Skin biopsies met clinical criteria for GWI for 42 (82%) and 24 of 42 (57%) were determined to have SFN. Four of 9 (44%) veterans without GWI had positive SFN biopsies, though this difference was not statistically significant (Table 1). Veterans with SFN but no GWI were not included in the further analysis.

Thirty-five veterans with GWI—18 with SFN and 17 without SFN—completed the COMPASS 31 (Table 2). COMPASS 31 data were not analyzed for veterans without GWI. Individual domain scores and the difference in COMPASS 31 scores for veterans with GWI and SFN vs GWI and no SFN (38.3 vs 37.8, respectively) were not statistically significant.

Sixteen of 24 veterans with GWI and SFN (67%) had ≥ 1 conditions that could potentially be responsible for SFN (Table 3), including 11 veterans (46%) with prediabetes/diabetes. Hyperlipidemia is only variably reported as a cause of SFN; when included, 19 (79%) of 24 of SFN cases were accounted for. We could not identify a medical explanation for SFN in 5 of 24 veterans (21%) with GWI, which were deemed to be idiopathic.

## DISCUSSION

Biopsy-confirmed SFN was present in more than half of our sample of veterans with GWI, which is broadly consistent with what has been reported in the literature.<sup>13,35-38</sup> In this clinical observation study, SFN was similarly prevalent in veterans with and without GWI; although it should be noted that biopsies only were obtained

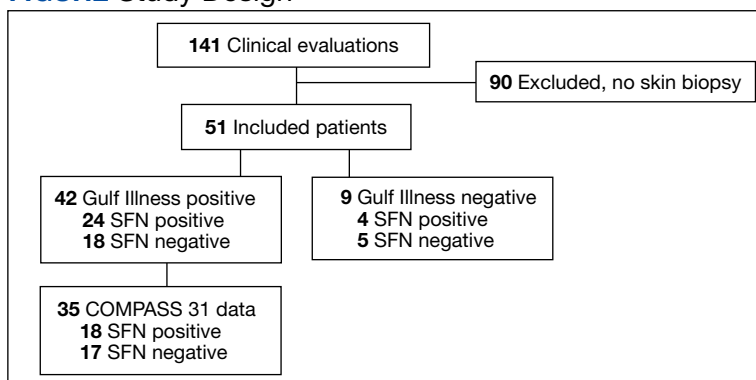
when there was a strong clinical suspicion for SFN. Almost half of patients with GWI did not have SFN, so our study does not support SFN as the underlying explanation for all GWI. Although our data cannot provide clinical guidance as to when skin biopsy may be indicated in GWI, work done in fibromyalgia found symptoms of dysautonomia and paresthesias are more specific for SFN and may be useful to help guide medical decision making.<sup>39</sup>

Veterans with GWI in our clinical sample reported a high burden of clinical symptoms conceivably attributable to ANS dysfunction. This symptom reporting is consistent with that seen in other GWI studies, as well as in other studies of SFN.<sup>4,5,7-9,14,15,34,38,40</sup> Our clinical sample of veterans with GWI found no differences in the ANS symptom reporting between those with and without SFN. Therefore, our study cannot support SFN alone as accounting for ANS symptom burden in patients with GWI.

Two-thirds of biopsy-confirmed SFN in our clinical sample of veterans with GWI could potentially be explained by established medical conditions. As in other studies of SFN, prediabetes and diabetes represented a plurality (46%). Even after considering hyperlipidemia as a potential explanation, about 21% of SFN cases in veterans with GWI still were deemed idiopathic.

Evidence supports certain environmental agents as causal factors for GWI. Neurotoxicants reportedly related to GWI include pesticides (particularly organophosphates and carbamates), pyridostigmine bromide (used during the Gulf War as a prophylactic agent against the use of chemical weapons), and low levels of the nerve agent sarin from environmental contamination due to chemical weapons detonations.<sup>1</sup> Some of these agents have been implicated in neuropathy as well.<sup>1,28-30</sup> It is biologically plausible that deployment-related exposures could trigger SFN, though the traditional consensus has been that remote exposure to neurotoxic substances is unlikely to produce neuropathy that presents many years after the exposure.<sup>41</sup> In the WRIISC clinical experience, however, veterans often report that their neuropathic symptoms predate the diagnosis of the associated medical conditions, sometimes by decades. It is conceivable that remote exposures may trigger the

**FIGURE** Study Design



Abbreviations: COMPASS 31, Composite Autonomic Symptom Scale 31; SFN, small fiber neuropathy.

condition that is then potentiated by ongoing exposures, metabolic factors, and/or other medical conditions. These may perpetuate neuropathic symptoms and the illness experience of affected veterans. Our clinical observation study cannot clarify the extent to which this may be the case. Despite these findings and arguments, an environmental contribution to SFN cannot be discounted, and further research is needed to explore a potential relationship.

### Limitations

This study's conclusions are limited by its observational/retrospective design in a relatively small clinical sample of veterans evaluated at a tertiary referral center for postdeployment exposure-related health concerns. The WRIISC clinical sample is not representative of all GWVs or even of all veterans with GWI, as there is inherent selection bias as to who gets referred to and evaluated at the WRIISC. As with studies based on retrospective chart review, data are reliant on clinical documentation and accuracy/consistency of the reviewer. Evaluation for SFN with skin biopsy is an invasive procedure and was performed when a high index of clinical suspicion for this condition existed, possibly representing confirmation bias. Therefore, the relatively high prevalence of biopsy-confirmed SFN seen in our clinical sample cannot be generalized to GWVs as a whole or even to veterans with GWI.

Assessment of autonomic dysfunction was based on COMPASS 31 symptom reporting by a small subset of the clinical cohort. Symptom reporting may not be reflective of

true abnormality in ANS function. Physiologic tests of the ANS were not performed; such studies could more objectively establish whether ANS dysfunction is more prevalent in GWI veterans with SFN.

Evaluation for all potential etiologic/contributory conditions to SFN was not exhaustive. For example, sodium channel gene mutations have been documented to account for up to one-third of all cases of idiopathic SFN.<sup>42</sup> For those cases in which no compelling etiology was identified, it is plausible that medical explanations for SFN may be found on further investigation.

Clinical assessments at the WRIISC were performed on GWVs  $\geq$  26 years after their deployment-related exposures. Other conditions/exposures may have occurred in the interim. What is not clear is whether the SFN predated the onset of any of these medical conditions or other putative contributors. This observational study is not able to tease out a temporal association to make a cause-and-effect assessment.

## CONCLUSIONS

Retrospective analysis of clinical data of veterans evaluated at a specialized center for postdeployment health demonstrated that skin biopsy–confirmed SFN was prevalent, but not ubiquitous, in veterans with GWI. Symptom that may be attributed to ANS dysfunction in this clinical sample was consistent with literature on SFN and with GWI, but we could not definitively attribute ANS symptoms to SFN. Our study does not support the hypothesis that GWI symptoms are solely due to SFN, though it may still be relevant in a subset of veterans with GWI with strongly suggestive clinical features. We were able to identify a potential etiology for SFN in most veterans with GWI. Further investigations are recommended to explore any potential relationship between Gulf War exposures and SFN.

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*Data analysis:* Shadiack, Gruber-Fox, Helmer.

*Drafting of manuscript:* Shadiack, Osinubi.

*Critical review of manuscript:* Gruber-Fox, Patrick-DeLuca, Cohen, Helmer.

## Author disclosures

The authors report no actual or potential conflicts of interest or outside sources of funding with regard to this article.

## Disclaimer

The opinions expressed herein are those of the authors and do not necessarily reflect those of *Federal Practitioner*, Frontline Medical Communications Inc., the US Government, or any of its agencies.

## Funding and ethics

This study was reviewed and approved by the Veterans Affairs New Jersey Health Care System Institutional Review Board (IRB# 01497). Funding provided by Veterans Affairs War Related Illness and Injury Study Center-New Jersey clinical resources; US Department of Veterans Affairs Health Services Research & Development (CIN 13-413). Poster presented virtually at the American Autonomic Society's annual meeting, November 2020.

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## APPENDIX Health Record Search for Potential Small Fiber Neuropathy Etiologies

Search location	Targets
Active problem list	Large fiber neuropathy, diabetes, prediabetes, impaired fasting glucose, metabolic syndrome, HIV, hepatitis C, paraproteinemia, multiple myeloma, monoclonal gammopathy of undetermined significance, autoimmune diseases, hypothyroidism, amyloidosis, paraneoplastic syndrome, cancer (other than squamous or basal cell skin cancer), vitamin B <sub>12</sub> deficiency, vitamin B <sub>6</sub> toxicity, and any language suggestive of alcohol abuse within the prior 5 years
Family history	Neuropathy in a first-degree relative
Medication list	Statins, antivirals, chemotherapeutic agents, linezolid, metronidazole, nitrofurantoin, flecainide, and isoniazid
Laboratory data	Hemoglobin A <sub>1c</sub> > 5.7, HIV antibody, hepatitis C antibody, serum protein electrophoresis, antinuclear antibody > 1:160, Sjögren's syndrome A or B antibodies greater than upper limit of normal, thyroid-stimulating hormone > 5 mIU/L, paraneoplastic antibodies, vitamin B6 greater than upper limit of normal, or vitamin B <sub>12</sub> > 200 ng/mL