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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 standard. 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 regional 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 43.0±18.6 years old. High erythrocyte sedimentation rate (ESR) and antinuclear antibody (ANA; ≥1:160 titer) were 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, Sjögren's and celiac autoantibodies. Together, these suggest the possibility of a specific association between iiSFPN and dysimmunity. ATR identifying diabetes, prediabetes, and hypertriglyceridemia were less common in iiSFPN than in the population and thus not associated with iiSFPN here. Reimbursement for the 6 most cost-effective iiSFPN-associated blood tests–ESR, ANA, C3, autoantibodies for Sjögren's and celiac, plus thyroid-stimulating hormone–was $99.57/person with 45.6% sensitivity for detecting 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

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INTRODUCTION

Distal peripheral polyneuropathy is highly prevalent and often disabling. The most common complaints are sensory. Many of these are 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 any 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 most 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 [3][**]. Neurological examination can be unrevealing in SFPN, since muscle bulk, strength, tendon reflexes, and sensations of touch, position, and vibration are preserved. Electromyography and surface nerve-conduction study (EMG/NCS) do not detect small-fiber potentials and thus these tests 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 [69]; it causes about half of SFPN in U.S. population-based studies [26]. The second largest group of SFPN patients, comprising 20–50% in recent series [19, 22, 26, 51, 69], is those with “initially idiopathic” or cryptogenic causes (here abbreviated as iiSFPN). They are the focus of the current study. The reason to try to identify underlying 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 then 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 most common occult causes [18]. In a recent study of patients with mixed distal polyneuropathies, screening led to potentially disease-modifying management changes in 25% [7].

Previously, objective confirmation of suspected SFPN required surgical biopsy of a sensory nerve, which 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 [11, 14, 17, 37]. Research application of skin biopsy and AFT has suggested that SFPN appears to be a common denominator underlying 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 [65]. And 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 [43]. Multiple groups have now reported that almost half of patients with fibromyalgia have objective evidence of underlying SFPN [2, 15, 23, 34, 42, 53, 58, 68]. Given that fibromyalgia affects 2–5% of the world's population [71], 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 [69], alcohol-related liver dysfunction [5], heavy-metal toxicity [36], deficiencies of vitamins B12 (cobalamin) and B1 (folate) [33, 60], hypothyroidism and hyperthyroidism [1, 47], paraproteinemia [74], sarcoidosis [24], and systemic autoimmune disorders including Sjögren's syndrome (SS) [49, 55], systemic lupus erythematosus [46], and celiac [6, 8, 64]. Infectious causes include human immunodeficiency virus [62], hepatitis C [10], leprosy [38], and Lyme disease [25]. Rare genetic variants underlie some familial and sporadic cases, with a Dutch SFPN cohort reporting 2.3% prevalence of SCN9A sodium-channel mutations [51].

Although insufficient screening risks missing potentially curable causes, 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 specific 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) [18]. 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 that 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 time and place cannot be globally generalized. This study has the advantages of having is 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 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 U.S. and some from across the U.S. 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 [17, 37] – 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 among these tests that had been performed within one 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 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-hour glucose value from 75-gram oral glucose tolerance testing (OGTT). Normality was interpreted according to American Diabetes Association (ADA) standards. Diabetes was defined by A1C ≥ 6.5%, fasting glucose ≥ 126 mg/dl or 2-hour OGGT value ≥ 200mg/dl. Pre-diabetes was defined by A1C ≥ 5.7% and < 6.5%, fasting glucose between 100–126 mg/dl, or 2-hour OGTT 140–199 mg/dl. Lyme disease definition 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-side, plus upper- and lower-body pain) [72], chronic headache [43], and other somatosensory symptoms (paresthesias, 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 U.S., 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 ± 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) in Table 2. If U.S. 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 ≥ 300% the prevalence in the best available population prevalence for us to label the medical condition tested for as potentially specifically associated with SFPN. The cost of screening to identify one abnormal blood-test result was calculated as 100/(% ATR × 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 ± 18.6 years (range 8–81 years), 70.3% were female and 94.9% were Caucasian. Among the 41 with results of EMG/NCS available, 27% of these studies 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 ABTR 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 0.0–5.5% for the 3 different blood tests analyzed. For prediabetes, between 15.0–25.0% had abnormalities on the different tests used to identify this. Among the patients with results of testing 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 in 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 6 tests for diabetes and pre-diabetes were less prevalent in the iiSFPN cohort than in the NHANES-surveyed U.S. population, which reported 5.8% prevalence of undiagnosed diabetes and 44.9% total prevalence of prediabetes among US

adults age 45–64 [40]. Occult diabetes and prediabetes were therefore far less common among studied iiSFPN patients than in the population.

In contrast, none among the 8 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-antiTTG) had ABTR prevalences below comparator population prevalences (Table 2). The prevalence 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 [21] as well as the 13.8% U.S. population prevalence for titer ≥ 1:80 [54]. The excess prevalence of both low and high TSH suggest associations not only with hypothyroidism but also with thyroiditis, which is often autoimmune [27]. Together, these findings suggest that occult dysimmune/inflammatory conditions may contribute to iiSFPN in this cohort.

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 were further specifically evaluated for sarcoidosis, with chest CT performed in 7. None among them 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. Although the reimbursement for each individual test varied by less than 10-fold, when the frequency of ABTR was factored in to estimate the cost of screening enough patients to obtain one abnormal test result, this cost 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 north eastern U.S. and 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 risk, 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

results are imprecise. This is unavoidable in studies that use population-based controls, but the other option of case-control studies can also be inaccurate due to their much smaller control samples. To compensate for this uncertainty, we took a very conservative approach of only reporting medical conditions tested for as potentially associated with iiSFPN when prevalences of ABTR were at least three times or 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 shown 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 in results from other cohorts into its conclusions. Another limitation is that MGH's electronic record only rarely specified if glucose measurements were 2-hour values from OGTT. Since we could definitively identify only eight 2-hour values, we did not include 2-hour values in the specificity analyses. Also, 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 U.S. 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 U.S. prevalence of diabetes in adults between 45–65 years old was 17.5%, of which 5.8% was undiagnosed/occult [40]. In contrast, the MGH iiSFPN cohort had a 5.5% prevalence by A1c (Table 2). Two other idiopathic neuropathy cohorts had higher rates of undiagnosed diabetes, e.g., 13% in Utah [60] and 9.2% in New York [19], but two others were lower, 1.7% in Michigan [7], and 3% in New York [13], so the overall importance of undiagnosed diabetes as a contributor to initially idiopathic SFPN remains uncertain. These prevalence differences might reflect social 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 [59, 61]. Its prevalence here (14.7%) and in all other U.S. neuropathy cohorts (6.1% and 22.7% in Michigan [7, 22], 11% in Ohio [32], 7% and 11% in New York [13, 19]), are all far below the NHANES-based U.S. population prevalences (e.g., 44.9% for adults aged 45–65) [40]. Plus, 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 [16]. The situation appears similar for hypertriglyceridemia. Although it increases the risk of diabetics developing polyneuropathy [63], prevalences in iiSFPN cohorts (24% here, 34% in Ohio [50]) do not exceed the 33% population prevalence [66].

Autoimmune neuropathies are divided into those associated with systemic or multi-organ autoimmunity, and nerve-specific conditions. Systemic lupus erythematosus [46], Sjögren's [55, 56], and celiac [6, 8, 9, 39, 64], are systemic or multi-organ autoimmune conditions that are thought to include SFPN, although odds ratios have not been determined. Serologic

markers for all 3 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 ≥ 1:160 (27.5%), with other surveys reporting 11% [50], 12.6% [22], and 4.6%.[60]. Similarly, the 9.8% prevalence of SS-autoantibodies here exceeds the 1.8% reported from New York [19], and the 7.5% prevalence of SS (test unspecified) from Milan [14]. 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 [56], 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 [22].

There are well-known large-fiber-specific autoimmune neuropathies where attack targets 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 [41]. It is logical that small-fiber-predominant autoimmune axonopathies should also exist, and we and others have reported cases, although these are not yet well-characterized [12, 43, 48, 57]. Dysimmunity may be a particularly common cause of neuropathy in children and young adults, since they lack most other risks [43, 48]. 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 [43].

There is an established association between monoclonal gammopathies and large-fiber demyelinating polyneuropathy, but the question of whether there is also an association with SFPN has not yet been examined. The 3.9% sample prevalence of monoclonal gammopathy in the population and rates from most other U.S. studies (3.0% in Utah [60], 4.0% in Michigan [22], 7.0% in New York [19]) are slightly higher than the 3.2% prevalence of MGUS in U.S. adults over age 50 even though they include patients under 50 [35]. Although inconclusive, this comparison suggests the need for a targeted study. 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 [33] and folate levels do not correlate with risk of POTS, which is a common symptom of SFPN [45]. Given the lack of evidence for an association here, plus the rarity of folate deficiency in other U.S. neuropathy cohorts (0%) [60] 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 [19] and 2% prevalences in Utah [60] are below population prevalence. We identified only one exception, the 6% prevalence reported from one New York study [13]. Both low and high TSH were overrepresented in the MGH study sample by an order of magnitude as compared to population prevalences. The American Academy of

Neurology and other groups do not recommend screening neuropathy patients for hypothyroidism [18, 22], 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 U.S.

We also analyzed the costs of screening (Table 3). Medicare reimbursement for the 3 tests recommended by the AAN [18] (glucose, B12 and SPEP/IFIX) was $42.97/person, and ≥ 6.8% of the MGH cohort would have at least one ABTR. The American Academy of Neurology endorsed screening panel (OGTT, B12, SPEP/IFIX, and ANA) [60] 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 2 most cost-effective and specifically SFPN-associated blood tests from the current analysis – ESR and ANA – was only $20.18/person, although these two tests alone would convey a higher 38.5% probability of detecting at least one abnormal test results in the MGH cohort, improving sensitivity plus reducing per-patient cost. Reimbursement for the 3 most cost-effective and specifically associated blood tests from the current analysis – ESR, ANA and C3 – was $36.56/person with 41.0% sensitivity for detecting one abnormal result in MGH cohort. Reimbursement for the 6 most cost-effective and specifically associated blood tests from the current analysis – ESR, ANA, C3, Sjögren's autoantibodies, celiac testing (IgA-antiTTG), and TSH – was $99.57/person with 45.6% sensitivity for detecting one abnormal result in MGH cohort.

Another consideration pertinent to cost-effectiveness is the "actionability" of each ABTR [7]. 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 [20], 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 prompts 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 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 normality and abnormal results for each test. Comprehensive reporting of these in future studies is encouraged to enable systematic review and pooling of results from multiple studies to add power and inform about even rare causes of initially idiopathic polyneuropathy.

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Table 1

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

First author	MI Periquet	RAC Hughes	AG Smith	EA De Sousa	G Devigili	J Bednarik	S Khan	MJH Peters	G Gallagher	K Farhad	**M.Lang**
Location of study	Ohio/USA	London/UK	Utah/USA	New York/USA	Italy	Czechia	Ohio/USA	The Netherlands	Michigan/USA	New York/USA	**MA/USA**
Year of publication	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**
Skin biopsy confirmation of SFPN	yes	no	no	yes	yes	yes	yes	yes	no	no	**yes**
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:											
A1C diagnostic for diabetes		not reported	not reported		not reported	not reported				not reported	**5.5%**
A1C diagnostic for prediabetes		not reported	not reported		not reported						**14.70%**
Fasting glucose for diabetes		not reported	3.7%		not reported		not reported				**0.0%**
Fasting glucose for prediabetes		not reported	7.5%		not reported	not reported	not reported				**25.0%**
Glucose tolerance test for diabetes		not reported	13%	3%	not reported	not reported	not reported			not reported	**0.0%**
Glucose tolerance test for prediabetes			not reported	11%	not reported	14.30%	not reported			not reported	

Random glucose for diabetes	0.0%										
Thyroid stimulating hormone	0.0%		0.0%	2%	not reported	not reported	10.3%	not reported	6.2%	0.7%	**6.2%**
Thyroxine (T4)	0.0%					not reported	not reported	not reported	4.1%		
Vitamin B12 (low)	0.0%		1.4%	6%		not reported	2.3%			1.4%	**1.5%**
Methylmalonic acid	not reported		not reported	not reported						not reported	
Homocysteine	not reported		not reported	not reported						not reported	
Vitamin B1										0.7%	
Vitamin B6 (high)			2.2%					4.5%		2.5%	
Vitamin B6 (low)										0.2%	
Vitamin C		not reported									
Vitamin E	0.0%	not reported									
Folate			0.0%			not reported					**2.0%**
Erythrocyte sedimentation rate	not reported		0.0%	not reported					22.3%	not reported	**28.0%**
Antinuclear antibodies (ANA)	11.0%		2.2%	not reported		not reported	not reported		12.6%		**27.5%**
Extractable nuclear antigen antibodies	not reported						not reported		not reported		
Anti-double stranded DNA				not reported					4.5%		
Anti-Smith antibodies				not reported							
Ribonucleoprotein antibodies				not reported						not reported	
Sjögren's AB (SS-A/Ro, SS-B/La)	not reported		0.7%	not reported	not reported				not reported	1.8%	**9.2%**
Celiac antibodies				6%	not reported		not reported			1.4%	**3.5%**
Antineutrophil cytoplasmic AB				not reported					12.0%	not reported	
Complement C3											**11.0%**
Complement C4											**15.7%**
Rheumatoid factor	not reported			not reported			not reported		5.0%	not reported	
ANCA									12.0%		
Cryoglobulins				not reported			not reported				
C-reactive protein				not reported					17.0%	not reported	**12.6%**
Protein immunofixation	6.8%		2.2%	6%	not reported	not reported	4.0%	2.3%		7.0%	**3.9%**
Quantitative immunoglobulins				not reported						1.4%	
Creatinine and/or blood urea nitrogen	0.0%					not reported					**2.5%**
High cholesterol	28%					70.2%					
High triglycerides	34%	not reported				not reported		1.1%			**24.7%**
Angiotensin converting enzyme				not reported			0.0%				**44.6%**
Liver function tests	not reported					not reported					**14.8%**
Hydroxyurea				not reported							
Copper										not reported	

HIV	0.0%			not reported			not reported	not reported			not reported	
Lyme disease				10%			not reported	not reported			0.3%	**8.7%**
Hepatitis A				not reported								
Hepatitis B				not reported			not reported				not reported	
Hepatitis C				not reported		not reported	not reported	not reported			not reported	**1.1%**
Syphilis	not reported						not reported					
Myelin-associated glycoprotein AB	0.0%			not reported		not reported	not reported				1.4%	
Ganglioside antibodies	not reported	not reported	0.0%	not reported							not reported	
Sulfatide antibodies	2.3%			not reported							0.30%	
Antineve antibodies	0.0%	not reported		not reported			not reported	not reported			not reported	
Paraneoplastic antibodies			0.7%				not reported				not reported	

Abbreviations: A1C = hemoglobin A1C, AB = antibodies, ANCA = antineutrophil cytoplasmic antibody, MA = Massachusetts, HIV = human immunodeficiency virus, PGP9.5 = protein gene product9.5, SFPN = small fiber polyneuropathy

Table 2
Prevalence of ABTR in the iiSFPN cohort and in comparator population data

Green shading indicates tests in which the prevalence of an ABTR in the iiSFPN cohort was ≥ 300% than the population prevalence. Yellow shading indicates tests in which the comparison yielded uncertain results because the prevalence of ABTR in the iiSFPN cohort was above but not greater than 300% of the population prevalence. Red shading indicates tests in which an ABTR was more common in the population than in the iiSFPN cohort. 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). “high” indicates that only values above the reference range were considered as abnormal. “low” indicates that only values below the reference range were rated as abnormal.

Test (definition of abnormal result)	Medical condition tested for	Prevalence of abnormal test result in sample (n)	Population prevalence of abnormal test result and source
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 [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 [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% for occult DM by A1C or OGTT in US age 45–64 [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]

Test (definition of abnormal result)	Medical condition tested for	Prevalence of abnormal test result in sample (n)	Population prevalence of abnormal test result and source
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 [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 [40]

Abbreviations: 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 hour oral glucose tolerance test, IFIX = immunofixation, SPEP = serum protein electrophoresis, IgA antiTTG = immunoglobulin A antibodies to tissue transglutaminase.

Table 3

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

The most cost-effective tests for screening (< $250 per one abnormal result) are highlighted in green, and tests with moderate screening costs (> $250 but < $500 per one abnormal result) are highlighted in yellow. Red highlighting indicates the least cost-effective tests (> $500 per one abnormal result). Fasting glucose and 2-hour OGTT to detect diabetes are not included since no patients had abnormal results thus screening costs would be infinite.

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