Value of thyroid and rheumatologic studies in the evaluation of peripheral neuropathy

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Summary

Peripheral neuropathy is a common disorder, often prompting an extensive initial laboratory evaluation. The initial evaluation is particularly challenging to primary care physicians and neurologists because of the broad differential diagnosis. Although screening thyroid and rheumatologic tests are frequently ordered, the diagnostic yield of these tests is unclear. Data from our institution were collected on patient demographics, clinical characteristics including warning signs suggestive of a diagnosis other than distal symmetric polyneuropathy, history of thyroid or rheumatologic disease, and laboratory tests ordered. Thyroid and rheumatologic screening tests are commonly ordered in the evaluation of peripheral neuropathy. Our findings suggest a low aggregate value of these tests based on low yield and infrequent changes in the suspected etiology or management of these patients.

Peripheral neuropathy encompasses a heterogeneous group of disorders, including distal symmetric polyneuropathy, multiple mononeuropathies, and demyelinating neuropathies, among many others. Peripheral neuropathy is a prevalent condition affecting approximately 2% of the general population and as many as 8% of those over the age of 55.^{1,2} Distal symmetric polyneuropathy (DSP) is the most frequently encountered form of peripheral neuropathy, typically presenting symmetrically in the feet with pain,

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numbness, paresthesias, or weakness. The American Academy of Neurology (AAN) recently published guidelines for the laboratory evaluation of DSP.³ Based on a systematic review of the literature, the AAN concluded that the tests providing the highest yield are fasting blood glucose levels, serum B12, associated metabolites (methylmalonic acid and homocysteine), and serum protein electrophoresis. For those with a sensory predominant neuropathy, a glucose tolerance test could be considered. However, the AAN guideline statement did not address other commonly ordered tests, such as thyroid and rheumatologic tests.

Although peripheral neuropathy is a common ailment, what constitutes an efficient evaluation remains obscure. An initial approach of ordering a wide variety of laboratory tests has disadvantages (e.g., excess cost and false-positive results) for the patient. To analyze the current practices of physicians, a recent survey was conducted which revealed substantial variation in testing both within and between provider types. Overall, neurologists indicate they would order many tests, including thyroid (92%) and rheumatologic studies (ranging from 21% to 75% over a variety of tests).⁴ Unfortunately, the cost of evaluations can be prohibitive, and physicians often order high-cost, low-yield tests rather than low-cost, high-yield studies.⁵ Despite the recent AAN recommendations and the publication of several clinical approaches to the evaluation of neuropathy, clinicians continue to order a wide variety of laboratory tests.³⁻⁷

In this study, we evaluated the frequency of abnormal thyroid or rheumatologic results in the setting of a diagnosis of peripheral neuropathy. When the tests were abnormal, we assessed the frequency that the test changed the suspected etiology or management. We hypothesized that the predictive factors of an abnormal test that impacted the care of these patients were presence of warning signs of an atypical neuropathy subtype and a history of thyroid or rheumatologic disease. This study was performed at a single tertiary care center and one of the main limitations is the possibility of referral bias, such that those individuals with true-positive laboratory abnormalities were identified and treated elsewhere.

METHODS

This was a single-center retrospective chart review, approved by the University of Michigan Institutional Review Board. Cases were identified by reviewing the electronic medical record of all new patients presenting to the University of Michigan Neuromuscular Clinic, a tertiary referral center, from January 1, 2007, through December 31, 2008. The inclusion criterion was a neuromuscular physician's diagnosis of peripheral neuropathy at the initial appointment. Exclusion criteria were evidence of compression neuropathy, traumatic neuropathy, or radiculopathy.

The following information was abstracted from the medical record: demographics, duration of symptoms, the presence of pain, presence of weakness on examination, any nerve conduction study abnormality, EMG evidence of denervation outside of the foot attributed to neuropathy, history of thyroid or rheumatic disease, and signs/symptoms of thyroid (e.g., weight changes, diarrhea/constipation, hair/skin changes) or rheumatologic disease (e.g., rash, joint swelling/redness, dry mouth/eyes, unexplained fevers/chills). Warning signs suggestive of an alternative neuropathy subtype other than DSP were also gathered, including acute or relapsing onset, motor-predominant symptoms, non-length-dependent symptoms, prominent autonomic

Table 1 Patient characteristics

Characteristics	No. (%) or median (IQR)
Age, y	63 (51–72)
Years since onset	3 (1–6)
Male	137 (60.9)
Neuropathy type	
DSP	145 (64.4)
Small fiber	52 (23.1)
DSP/small fiber	9 (4.0)
Chronic demyelinating neuropathy	9 (4.0)
Multiple mononeuropathies	5 (2.2)
Motor neuronopathy	3 (1.3)
Sensory neuronopathy	2 (0.9)

Abbreviations: DSP = distal symmetric polyneuropathy; IQR = interquartile range.

features, and asymmetry.⁸ The suspected etiology and neuropathy subtype were extracted from the medical record.

Laboratory tests were ordered at the discretion of the evaluating clinician at the University of Michigan. Any available laboratory tests ordered by the referring physician were also included. The results of screening blood tests for thyroid (thyroid-stimulating hormone [TSH] and thyroxine [free T4]) and rheumatologic conditions (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], antinuclear antibody [ANA], antineutrophil cytoplasmic antibodies [ANCA], anti-double-stranded DNA [dsDNA], rheumatoid factor [RF], anti-Ro [anti-SSA], anti-La [anti-SSB], or extractable nuclear antigen antibodies) were identified and documented as normal or abnormal, based on established laboratory standards at the University of Michigan. When test results were abnormal, we documented whether the test changed the suspected etiology or management of the patient. A patient was classified as having a change in management if it was documented that a medication change was performed as a result of an abnormal test.

Descriptive statistics were used to summarize the data.

RESULTS

From January 1, 2007, to December 30, 2008, there were approximately 1,600 new patient presentations to the University of Michigan Neuromuscular Clinic, with 225 patients meeting inclusion criteria (table 1). Median age was 63 years (interquartile range [IQR] 51–72). The median time from symptom onset to evaluation in our clinic was 3 years (IQR 1–6). DSP (145 patients, 64.4%), followed by small-fiber-predominant neuropathy (51 patients, 22.7%), were the most common neuropathy subtypes.

After diagnostic testing, the most common etiologies suspected by the treating physician were as follows: impaired glucose tolerance (51 patients, 22.7%), diabetes (48 patients, 21.3%), and idiopathic (44 patients, 19.6%) (table 2). Autoimmune etiology was suspected in 13 patients (5.8%) with known rheumatologic disease. Twelve patients without known rheumatologic disease were suspected to have neuropathy secondary to autoimmune etiology. Thyroid dysfunction was suspected as a contributing cause in 3 patients (0.9%).

Pain (72%) was the most commonly documented symptom, followed by weakness (29.8%). Warning signs of neuropathy subtypes other than DSP were noted among 16.9% of the patient cohort. Thyroid dysfunction (defined by history or symptoms) was documented in 15.6% of the patients, while rheumatologic disease was documented in 12.4%.

Table 2 Suspected posttest etiology

Etiology	Patients with a single suspected etiology, n (% out of 201 patients)	Patients including those with 2 or more suspected causes, n (%)
Diabetes	44 (21.9)	48 (21.3)
Idiopathic	44 (21.9)	44 (19.6)
Impaired glucose tolerance	37 (18.4)	51 (22.7)
Genetic	20 (10)	26 (11.6)
Chemotherapy/toxic	15 (7.5)	19 (8.4)
Known rheumatologic disease	10 (5.0)	13 (5.8)
Autoimmune (no previous disease)	10 (5.0)	12 (5.3)
MGUS or anti-MAG	8 (4.0)	10 (4.4)
EtOH	4 (2.0)	9 (4.0)
Renal failure	4 (2.0)	5 (2.2)
Other	3 (1.5)	4 (1.8)
B12	2 (1.0)	6 (2.7)
Thyroid	0 (0)	3 (1.3)

Abbreviation: MGUS = monoclonal gammopathy of undetermined significance.

Of the 225 patients, 77.8% had at least one abnormality on nerve conduction studies. Demyelinating features were noted in 8.4%. Denervation outside the foot was noted on EMG in 34.2%.

Thyroid studies

Thyroid screening was performed in 195 (86.7%) patients. Screening thyroid function tests were abnormal in 14 (7.2%) patients (table 3). TSH was abnormal in 12 of 195 (6.2%) screened patients, while free T4 was abnormal in 2 of 49 (4%). One patient with an abnormal free T4 (without a history or symptoms of thyroid disease) was diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy on the basis of clinical presentation and nerve conduction studies. The other patient with an abnormal free T4 had a known history of hypothyroidism. No changes were made to the suspected etiology or management of either patient based on these tests. Eight of the 12 patients with an abnormal TSH screen had a history of thyroid disease. Of the 4 patients without a history of thyroid disease, 2 patients had neuropathy attributed to active and known rheumatologic disease and 2 patients had neuropathy attributed to diabetes or impaired glucose intolerance. The treating physicians did not change the suspected diagnosis as a result of the abnormal tests due to 2 main factors. First, several patients with a history of hypothyroidism were already suspected to have a contribution from hypothyroidism. Second, the remaining patients were suspected and found to have alternative causes. In 3 patients with known severe hypothyroidism, the TSH was found to be markedly abnormal, and the treating neurologist recommended follow-up with the primary physician for changes in thyroid replacement dosing (table 4).

Rheumatologic studies

At least one rheumatologic study was abnormal in 31.3% (68 of 217) of screened patients (table 3). The most frequently abnormal rheumatologic laboratory studies were ESR (22.3%), CRP (17.0%), ANA (12.6%), and ANCA (12.0%) (table 3). Despite the frequency of abnormal rheumatologic tests, the suspected etiology or treatment was only changed in 3.2% (7 of 217) of patients (see table 4 for detailed information on these 7 patients). All of

Table 3 Yield of thyroid and rheumatologic tests in the evaluation of peripheral neuropathy

Test	Abnormal/total (%)
Composite thyroid tests	14/195 (7.2)
TSH	12/195 (6.2)
Free T4	2/49 (4.1)
Free T3	0/3 (0)
Composite rheumatologic tests	68/217 (31.3)
ESR	35/157 (22.2)
CRP	8/47 (17.0)
ANA	24/191 (12.6)
ANCA	6/50 (12.0)
RF	6/120 (5.0)
Anti-dsDNA	3/66 (4.5)
SSA, SSB + ENA	3/135 (2.2)

Abbreviations: ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody; CRP = C-reactive protein; dsDNA = double-stranded DNA; ENA = extractable nuclear antigen; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor; TSH = thyroid-stimulating hormone.

the patients in whom an abnormal test resulted in a management change had the presence of a warning sign for rheumatologic disease, a neuropathy subtype other than DSP, or a history of rheumatologic disease. In 3 of those patients, the tests confirmed the clinician's high degree of suspicion of a rheumatologic cause of the neuropathy. In one patient, the test led to a nerve biopsy and immunosuppression but the patient did not improve. In another patient, the rheumatologic test led to an incorrect diagnosis before an eventual diagnosis of familial amyloidosis. Two other patients were lost to follow-up soon after diagnostic tests were completed.

DISCUSSION

An efficient and effective approach to peripheral neuropathy is needed. Excess tests have substantial downsides including costs and patient inconveniences from false-positive results leading to unnecessary additional diagnostic tests and treatments. Testing for thyroid and rheumatologic disease in peripheral neuropathy patients has nearly become a routine practice.⁴ In this study of neuropathy patients who presented to an academic neuromuscular clinic, we found that screening for the presence of thyroid or rheumatologic disease in the absence of warning signs of an atypical neuropathy or a history suggestive of thyroid/rheumatologic dysfunction is low yield. No high-level evidence exists to support the routine use of these tests in DSP. Care must be taken to avoid generalizing the lack of utility of these tests to all patients with peripheral neuropathy, especially those patients with warning signs of an atypical neuropathy or warning signs of thyroid or rheumatologic dysfunction.

Our study builds on prior research that suggests low value to routine thyroid screening in peripheral neuropathy. In a recent study of 138 patients with a sensory predominant neuropathy, 81% of patients received a TSH study, yet none had an abnormal result.⁶ Similarly, our results demonstrate that thyroid studies are commonly ordered, but infrequently abnormal. Our study goes one step further to illustrate that when the result is abnormal, it never changed the suspected etiology. In contrast, multiple studies have investigated the presence of neuropathy in those with known hypothyroidism or hyperthyroidism and have found a significant proportion affected.^{9–11} However, these studies do not address whether patients

Table 4 Patients with a change in etiology or management of neuropathy based on rheumatologic or thyroid tests

Patient	History of rheum/thyroid disease	Etiology pretest (neuropathy subtype)	Warning sign	Laboratory data	Etiology posttest	Intervention/treatment
1	RA/SLE	RA/SLE (DSP)	None	dsDNA, ESR, ANA	RA/SLE	IV Cytoxan and rituximab initiated
2	No	PNS vasculitis (multiple mononeuropathies)	Asymmetry	ANCA	P-ANCA mononeuritis multiplex	Initiated Cellcept
3	Raynaud	PNS vasculitis (multiple mononeuropathies)	Asymmetry, acute onset, motor predominant	ANA, RF	Idiopathic/inflammatory	Nerve biopsy negative; treated with prednisone with no significant improvement
4	No	Inflammatory neuropathy (small-fiber)	Asymmetry, autonomic symptoms	ANA, CRP	Sjögren syndrome	Sural nerve biopsy, salivary gland biopsy positive, trial of prednisone, eventually Cellcept was initiated
5	No	Inflammatory neuropathy (DSP)	Motor predominant	SS-B	Familial amyloidosis (SS-B temporarily led to a false diagnosis of Sjögren neuronopathy)	Nerve and lip biopsies, genetic testing
6	No	CIDP vs PNS vasculitis (multiple mononeuropathies)	Asymmetry	ANCA	CIDP vs ANCA vasculitis	Trial of prednisone, recommended nerve biopsy but lost to follow-up
7	No	Inflammatory (sensory neuronopathy)	Acute onset	ANA	Inflammatory	Lost to follow-up after testing
8	Hypothyroid	Hypothyroid/impaired glucose tolerance (small fiber)	None	TSH	Impaired glucose tolerance (possible contribution from hypothyroidism)	Recommended follow-up with PCP for thyroid dose adjustment
9	Hypothyroid	Hypothyroid/impaired glucose tolerance (DSP)	None	TSH	Impaired glucose tolerance (possible contribution from hypothyroidism)	Recommended follow-up with PCP for thyroid dose adjustment
10	Hypothyroid	Hypothyroid/DM (DSP)	None	TSH	DM (possible contribution from hypothyroidism)	Recommended follow-up with PCP for thyroid dose adjustment

Abbreviations: ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CRP = C-reactive protein; dsDNA = double-stranded DNA; DSP = distal symmetric polyneuropathy; ESR = erythrocyte sedimentation rate; PCP = primary care physician; PNS = peripheral nervous system; RA = rheumatoid arthritis; RF = rheumatoid factor; SLE = systemic lupus erythematosus; TSH = thyroid-stimulating hormone.

with otherwise subclinical or undiagnosed thyroid dysfunction develop neuropathy. It is possible that mild thyroid dysfunction is thought to be insignificant by some clinicians, and therefore does not lead to a change in management. Additionally, the prevalence of thyroid abnormalities in our patient cohort was similar to a reference range from a healthy population of a comparable age range.¹² In contrast, impaired glucose tolerance is found at a higher frequency in patients with peripheral neuropathy than in the general population.¹³ Our study provides additional evidence that screening for thyroid dysfunction in all patients with peripheral neuropathy is likely unnecessary.

In comparison to thyroid studies, rheumatologic screening laboratory studies were also frequently ordered, but the yield was higher. However, the proportion of positive results was generally comparable to population-based studies of healthy individuals. Rheumatologic tests have

Rheumatologic tests have low specificity, especially in older populations, which is also the subgroup of the population with the highest incidence of peripheral neuropathy.

low specificity, especially in older populations, which is also the subgroup of the population with the highest incidence of peripheral neuropathy. In fact, the only test with a significantly higher yield than reported in healthy control populations was ANCA, with 12% abnormal tests in our patients compared with 2.2% in a healthy elderly population.¹⁴ However, this test only altered the etiology or management in 2 patients in our cohort, both of whom had evidence of an atypical neuropathy. The other rheumatologic tests were positive at a proportion similar to that found in older populations. For example, in our study, 12.6% of patients screened positive for ANA. By comparison, one group demonstrated a positive ANA in 36% of an elderly population.¹⁵ In our cohort, 5% of patients tested positive for RF and 4.5% for dsDNA, compared to 14.1% for both in an elderly Greek population.¹⁶ Furthermore, SSA was abnormal in 2.2% of our cohort, compared to a positive test in 1.6% of a healthy population.¹⁶ ESR and CRP were abnormal in 22.2% and 17% of our cohort, respectively. Previous studies have demonstrated an upward trend of values of nonspecific markers of inflammation such as ESR (abnormal in 25%–45% of those older than 50) and CRP (abnormal in 10%–30% of those older than 50).^{17,18} Importantly, abnormal rheumatologic tests rarely changed the etiology or management of these patients. All 7 of the patients where the test was informative had warning signs of an atypical neuropathy, a rare neuropathy subtype, or known rheumatologic disease. Since rheumatologic tests have a similar yield in our cohort compared with healthy populations and rarely change the suspected etiology or management, these studies should not be used as a routine screening tool in the absence of a reason to suspect an atypical neuropathy.¹⁹

The yield of most rheumatologic tests in patients with peripheral neuropathy has not been studied previously. A previous study of individuals with sensory predominant neuropathy demonstrated abnormal ANA testing in 3% of patients; however, this is less than what we and other population-based studies have documented.⁶ We also showed that this test does not alter the etiology or management in those without reasons to suspect an atypical neuropathy. Our study is the first to investigate the yield of other frequently ordered rheumatologic tests with results similar to that observed with the ANA and the first to evaluate the impact of testing on the etiology and management.

This study was limited by its single-center, observational design. There are inherent limitations to interpreting the work and documentation of other clinicians. Additionally there was no control population in which to compare the yield of the thyroid and rheumatologic tests. All patients in this study were seen at a tertiary care center; therefore, the results may not be generalized to other populations. As a tertiary referral center, most patients had previously laboratory testing, which likely resulted in a referral bias.

An efficient approach to the evaluation of peripheral neuropathy is necessary in the current health care climate, both due to rising health care costs, and in an effort to limit false-positive results leading to unnecessary additional diagnostic treatments. In fact, the Institute of Medicine estimates that the single highest driver of wasteful health care spending is unnecessary services.²⁰ Identifying those patients who would most benefit from specific diagnostic tests, such as with a clinical decision support tool, is one way to increase the efficiency and effectiveness of care in this population. In this study, we show that thyroid and rheumatologic tests rarely change the suspected etiology or management in those without warning signs, an atypical neuropathy

subtype, or a history of one of these diseases. While these tests still have a role in some patients with peripheral neuropathy, these studies probably should not be part of routine screening tests for all patients with DSP. We have altered our practice in the evaluation of DSP, but given the limitations discussed above, we do not want overstate these conclusions and generalize to all patients. Future studies are needed to investigate the role of other tests in the evaluation of peripheral neuropathy including the effect of these tests on patient outcomes.

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