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The Evaluation of Distal Symmetric Polyneuropathy: A Physician Survey of Clinical Practice

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Abstract

Objective—To define current clinical practice in the evaluation of distal symmetric polyneuropathy (DSP).

Design—Using a modified Dillman method, surveys were sent to 600 internists, 600 neurologists, and 45 neuromuscular specialists selected from the AMA Physician Masterfile. Survey questions pertained to which tests providers would order in the following three scenarios: 1) the initial evaluation of DSP, 2) additional tests if the initial evaluation was unrevealing, and 3) patients with diabetes. T-tests were used to compare the number of tests ordered by physician type and chi-square tests to compare proportions of tests ordered.

Setting—National survey of physicians

Participants—Internists and neurologists

Results—The response rate was 35%. Overall, many tests are ordered in the full evaluation of DSP (16.5 ± 7.2), and there is substantial variation within and between provider types. Internists

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Author contributions:

Dr. Callaghan was involved in development and distribution of the survey, the statistical analysis and wrote the manuscript. Dr. Kerber helped with statistical interpretation and contributed to the manuscript. Dr. Fendrick contributed to the manuscript. Ms. Smith was involved in maintaining the database and contributed to the manuscript. Dr. Feldman was involved in the planning of the project, interpretation of the statistical analysis, and contributed to the manuscript.

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planned to order fewer tests (14.5 ± 6.1) than neurologists (17.5 ± 7.9) ($p < 0.0001$). Regarding the glucose tolerance test (GTT), substantial differences were found between physician types, with neurologists and neuromuscular specialists ordering this test more frequently than internists (28.6% and 72.3% versus 4.1%, respectively). A brain and/or spine MRI was ordered by 19.8% of internists and 12.9% of neurologists.

Conclusions—Practice intent for the evaluation of DSP is highly variable and differs widely from the supporting evidence. A high yield test, the GTT, is rarely utilized; whereas, MRIs are likely over-utilized in this disorder of peripheral nerves. Research that defines the optimal evaluation of DSP has the potential to result in more efficient care.

Introduction

Peripheral neuropathy is a common and disabling condition that is diagnosed and evaluated by both internists and neurologists^{1–3}. Distal symmetric polyneuropathy (DSP) is the most common type of neuropathy, accounting for the majority of cases^{4,5}. Many underlying disorders cause or are associated with DSP, with diabetes leading the list^{4,6}. Disappointingly, despite an exhaustive evaluation, many patients are left without a definitive diagnosis^{7,8}.

A systematic review performed by the American Academy of Neurology (AAN) found that fasting glucose, serum protein electrophoresis (SPEP), and B12 tests have the highest yield in the evaluation of DSP⁹. The accompanying practice parameter statement also recommended that if the fasting blood sugar is normal, then the glucose tolerance test (GTT) may be considered especially in those with a sensory and and/or painful neuropathy⁹. However, this review did not address the use of many other commonly ordered laboratory tests for this condition as information is lacking on their utility.

In this study, we sought to investigate physician practices in the evaluation of DSP. One of the goals was to identify the degree of variation of practice, because substantial variation offers compelling evidence of the opportunity to improve efficiencies in healthcare¹⁰. Furthermore, we wanted to identify tests that are inappropriately utilized based on current evidence and to define which tests are in need of further study. The ultimate goal is to define the most efficient way to evaluate patients with this common, disabling condition.

Methods

Survey

We developed an eight question survey that pertains to the diagnostic evaluation of DSP. A comprehensive list of tests ordered for this condition was created based on an extensive literature review. These 47 tests included the following categories: hematology/chemistry, diabetes, vitamins, paraprotein, rheumatology, infections, immunology, radiology, electrodiagnosis, and pathology. The survey presented physicians with three common clinical scenarios (see eDocument1) and asked them to select the tests they would order for each scenario. The first scenario was regarding the initial evaluation of DSP with classic description of the condition, no clear cause from the clinical history, and the label of DSP. The second scenario was regarding additional testing if the initial evaluation was

unrevealing. The final scenario was regarding the evaluation specifically in patients with DSP and a history of diabetes. For each test, we also asked physicians to report which they considered reliable and valid.

Sampling design

The American Medical Association (AMA) Masterfile was used to sample physicians for the survey. We first excluded retired physicians, those with addresses outside the United States, and those with pediatric specialties and subspecialties. A random sample of 600 internists, 600 neurologists, and 45 neuromuscular specialists was selected. However, self-identification of specialty by responders was used for classification of provider type. For our power calculation we assumed a 35% response rate. Anticipating 210 measurable responses per group would provide 95% confidence intervals of $\pm 4\text{--}6\%$ for binary response variables with 86% power to detect 15% point differences between physician subgroups¹¹.

Surveys were mailed to each sampled physician. A modified Dillman method was used which entailed 4 mailings separated by 2 week intervals¹². The first mailing was a pre-notice letter followed by the survey with a \$2 incentive. The third mailing was a reminder postcard followed by a replacement survey. Demographics on non-responders were obtained from the AMA Masterfile.

Statistical analysis

Statistical analyses comparing internist versus neurologist responses were based on t-tests (unpaired, two-sided) and chi-square tests. Negative binomial regression models were used to evaluate for associations between provider characteristics and number of all tests ordered. Additionally, logistic regression models were designed to examine the association between provider characteristics and those who ordered 3 or 4 of the AAN recommended tests compared to those who did not. All statistical analyses were performed with SAS 9.2.

The University of Michigan's IRB approved this study.

Results

The overall response rate was 35% (429 of 1245). After excluding those with returned mailings due to wrong address, the participation rate was 39%. Neurologists were more likely to respond than internists ($p<0.0001$) (Table 1). All other demographic variables were similar between non-responders and responders including age, gender, degree, years since graduation, region of the country, and metropolitan size.

Population (Table 1)

The mean age of responders was 47.4 years old (SD 11.6) and 29.2% were female. Mean years since medical school graduation was 19.8 years (SD 12.1). Of the 429 returned surveys, 40.1% were completed by internists ($n=210$), 49.0% by neurologists ($n=172$), and 11.0% by neuromuscular specialists ($n=47$), 19 were classified based on the AMA Masterfile and 28 based on survey self-identification. Most respondents (94.6%) had M.D. degrees. The distribution between regions of the country was evenly distributed, whereas the vast

majority was from physicians who practiced in areas with a metropolitan size of greater than 250,000. Most respondents (61.1%) reported that neuropathy patients account for 1–10% of their patients. Another 35.1% of respondents reported that >10% of the patients they see have neuropathy. Regarding practice setting, 43.7% of respondents work in a private practice setting, 28.6% at a university, and 11.0% in a non-university teaching hospital.

Initial evaluation of DSP in those with no clear cause by history (Scenario 1, Figure 1A)

Of the 47 tests presented in the survey, internists indicated the intent to order 10.6 tests (SD 4.5) in the evaluation of DSP compared with 12.2 (SD 5.4) for neurologists and 13.3 (SD 5.4) for neuromuscular specialists ($p=0.002$, all comparisons are between internists and neurologists) (Table 2). Tests that were frequently ordered by all three physician groups included B12 levels (93.0%), CBC (85.6%), TSH (85.6%), Panel 7 (84.9%), Hemoglobin A1C (71.8%), and LFTs (62.0%). There was a significant disparity regarding the use of the GTT with 2.3% of internists indicating intent to order this test compared with 16.7% of neurologists and 34.0% of neuromuscular physicians ($p<0.0001$) (Figure 1A). Similarly, intent to order EMG/NCS was substantially higher among neurologists and neuromuscular specialists (74.8% and 89.4%, respectively) compared with internists (28.5%, $p<0.0001$). SPEP and immunofixation were both ordered more frequently by neurologists (68.1% versus 28.5% and 36.7% versus 7.6% respectively, $p<0.0001$). Internists ordered the following tests more frequently than neurologists: fasting glucose (76.7% versus 58.1%), urinalysis (37.2% versus 10.0%), and chest x-ray (14.0% versus 7.6%). Neurologists ordered rheumatologic and infectious tests more frequently than internists, with the exception of HIV and hepatitis B and C, but only the ESR and ANA were indicated in more than 50% of patients (62.9% of neurologists indicated would order ESR and 51.9% would order an ANA). Very few physicians of any type ordered lumbar puncture (1.9%), skin biopsy (1.6%), sural nerve biopsy (1.2%), MRIs of the brain (1.6%) or spine (3.7%), genetic testing (0.5%), or immunologic tests (anti-GM1 (3.3%), anti-sulfatide (1.9%), anti-MAG (4.2%), paraneoplastic antibodies (4.4%), and celiac screen (3.7%) in the initial evaluation of DSP.

Full evaluation of DSP when initial work up is unrevealing (Scenario 1 plus 2, Figure 1B)

When the initial work-up of DSP is negative, internists indicated that they would order a total of 14.5 tests (SD 6.1), neurologists 17.5 (SD 7.9), and neuromuscular specialists 18.7 (SD 6.4) in the full evaluation of DSP ($p<0.0001$) (Table 2). In this scenario, the disparity in use of the GTT by physician type increased as only 4.1% of internists would order the test compared with 28.6% of neurologists, and 72.3% of neuromuscular specialists ($p<0.0001$). Nearly 100% of physicians would order either a fasting glucose, HA1C, or a GTT.

Nearly 1 in 5 (19.8%) internists indicated intent to order an MRI of the brain and/or spine in the full evaluation of DSP (scenario 1 plus 2) (MRI brain 8.1% and MRI spine 15.7%). MRI use was less frequent among neurologists (12.9% total, MRI brain 3.3% and MRI spine 11.9%) and neuromuscular specialists (8.5%). EMG/NCS were ordered by 67.4% of internists, 92.9% of neurologists and 100% of neuromuscular specialists ($p<0.0001$). Tests that were rarely ordered as part of the initial evaluation that were much more frequently ordered after initial testing was normal were heavy metal testing (36.4%) by both types of

physicians and all immunologic tests (13–30%), genetic testing (10.0%), skin biopsies (15.2%), sural nerve biopsies (13.8%), and lumbar puncture (12.9%) by neurologists.

Considering the AAN recommended tests (fasting glucose, SPEP, B12, and GTT), only 2.3% of internists and 17.1% of neurologists indicated they would order all four ($p<0.0001$). Approximately 40% of physicians ordered three tests and an additional 30–40% would order two (Figure 2).

Evaluation of DSP in those with diabetes

Internists indicated that they would order a mean of 6.5 tests (SD 4.4), neurologists 6.6 (SD 4.8), and neuromuscular specialists 9.1 (SD 5.6) ($p=0.94$) (Table 2). All physicians frequently indicated that they would order a CBC, Panel 7, LFTs, and TSH tests. Neurologists and neuromuscular specialists (42.9% and 76.6%, respectively) were much more likely to order an EMG/NCS compared with internists (22.1%) ($p<0.0001$). Neurologists also ordered B12 levels (72.4% versus 57.0%), SPEP (31.0% versus 8.1%), and immunofixation (18.6% versus 3.5%) more frequently than internists. Internists were much more likely than neurologists to order a H_{A1C} (91.9% versus 68.1%), urinalysis (25.6% versus 6.7%), and/or chest x-ray (6.4% versus 1.9%). The remainder of tests were ordered only rarely.

Reliability and validity

More internists considered the GTT to be unreliable and invalid than neurologists (12.0% versus 5.2% and 6.4% versus 2.6%). Other tests with significant concerns for reliability and validity (defined as greater than 15% of physicians) included the ESR, CRP, vitamin E, ACE, Lyme, and MRI of the brain and spine. Physicians were also concerned with the validity of the rheumatoid factor and ANA tests. Internists more often indicated concern regarding the validity of skin biopsy (10.2% versus 4.6%) and sural nerve biopsy (9.6% versus 4.7%) than neurologists.

Provider characteristics

To determine which provider characteristics are associated with the number of tests ordered and the number of AAN tests ordered, two regression frameworks were utilized (Table 3). Variables included age, years since graduation, gender, metropolitan size where the physician practices, region of the country, specialty, degree, practice setting, and frequency of neuropathy patients in the physician's practice. For total number of tests ordered in the full evaluation, there was a significant association with specialty as neurologists were 17% more likely to order tests (OR=1.17, 95%CI 1.02–1.34) in fully adjusted regression models. Similarly, for the number of AAN tests ordered, the only significant association was physician specialty with neurologists and neuromuscular specialists ordering 3 or 4 AAN recommended tests more often than internists (OR=1.73, 95%CI 1.08–2.75 and 5.46, 95%CI 1.69–17.68). None of the other provider characteristics were significantly associated with number of all tests or the number of AAN tests ordered.

Discussion

Many tests are ordered in the evaluation of patients of patients with DSP, and there is substantial variation in care within and between physician groups. Despite high numbers of tests, the tests with the highest diagnostic yield are frequently omitted. Furthermore, the GTT, a high yield, low cost test is rarely utilized whereas MRI, a low yield, high cost test is likely over-utilized¹³⁻¹⁶. More research is needed to define the most effective and efficient approach in the evaluation of DSP.

Considerable within physician type variation is demonstrated by the large standard deviations for the number of tests ordered under each scenario. There is also substantial between physician group variation as revealed by the difference in test utilization comparing internists and neurologists. A recent report from the Institute of Medicine identified scientific uncertainty as one of the key drivers of rising health care costs in the United States and suggested consistency of treatment and/or evaluation as a possible solution¹⁰. Furthermore, high utilization of resources does not necessarily lead to better health outcomes, in fact the opposite pattern has been observed¹⁷. Therefore, efforts to identify the reasons for the variation in care of these patients are essential.

In all three clinical scenarios presented, neurologists ordered significantly more tests than internists. In fully adjusted regression models, the only variable significantly and independently associated with ordering more tests was specialty with neurologists ordering more tests compared to internists. The fact that neurologists order more tests is not surprising, since specialists tend to order more tests, and the patients they evaluate tend to be more complicated with more severe symptomatology.

In addition to a higher number of overall tests, neurologists also ordered more of the high yield tests (fasting glucose, SPEP, B12, and GTT), which are supported by recent AAN diagnostic recommendations for DSP. However, only a small number of physicians order all four tests with 57.6% of internists and 41% of neurologists ordering 2 or less. Of these tests, the GTT showed the most disparity between provider types. While only a few internists indicated they would order this test, almost a third of neurologists and over 70% of neuromuscular specialists include the GTT as part of the full work up of DSP⁹. The low utilization of this test may be in part due to the controversy surrounding impaired glucose tolerance as a cause of neuropathy^{14,16,18-20}. Furthermore, while the Diabetes Prevention Program demonstrated that an intense diet and exercise regimen help prevent progression to diabetes in this population, this intervention is not easily available to most patients and there is no definitive data on prevention or treatment of neuropathy²¹. On the other hand, two studies have shown that patients with idiopathic neuropathy have a much higher prevalence of impaired glucose tolerance than expected based on literature based controls^{14,16}. These results in conjunction with work demonstrating improvement in nerve fiber density in patients with IGT and neuropathy receiving diet and exercise, support IGT as a potentially common and treatable cause of neuropathy²². However, more definitive studies are needed to firmly establish IGT as a cause of neuropathy, and to make more conclusive recommendations regarding the GTT as a screening test in patients with DSP.

Surprisingly, a significant number of physicians indicated that they would order an MRI of the brain and/or spine in the full work up of a patient with neuropathy. In the survey scenarios, physicians were presented with a standard description of DSP with the diagnosis, and still MRIs were ordered by 1 out of 6 physicians. Internists were much more likely to indicate ordering MRIs, which may in part result from a lack of confidence in their ability to localize symptoms to the peripheral nerves. However, a higher than expected proportion of neurologists also ordered MRIs. While structural lesions of the brain and/or spine can mimic distal symmetric neuropathy, the survey scenarios were designed to specifically discourage concern for any disorder other than DSP. Since DSP affects the peripheral nervous system, imaging of the central nervous system does not seem indicated in this patient population and thus may represent a target for future efficiency improvements.

Electromyography was a frequently ordered test by all physician types in the evaluation of DSP. Neurologists were more likely to order this as part of the initial work up and in patients with diabetes, but most physicians believe that this test should be a part of the full evaluation of DSP. The high utilization is likely because electrodiagnostic studies can provide more objective evidence of neuropathy and identify those with demyelinating features. However, given that this test has important downsides (e.g., cost, time, patient discomfort), further research is needed to define the role of this diagnostic test in routine DSP presentations.

The SPEP and immunofixation tests are also ordered at differing rates depending on specialty. Neurologists are much more likely to order both tests, while internists rarely order an immunofixation test. The SPEP alone is much less sensitive than when done in conjunction with an immunofixation, and therefore, both tests should be performed when there is suspicion of an underlying bone marrow disorder^{23–25}. Evidence exists that patients with neuropathy have an increased prevalence of abnormal SPEP results especially in those with demyelinating neuropathy²⁶. However, neuropathy is a common condition and current evidence is unclear regarding the utility of routine SPEP and immunofixation testing in all patients with DSP.

Despite variations in clinical practice within this patient population, there are many tests that most physicians order. These include CBC, Panel 7, LFTs, TSH, B12 levels, and at least one test to evaluate for diabetes (fasting glucose, HA1C, and/or GTT). Although no evidence exists to support the use of CBC, Panel 7, LFTS, and TSH, these tests have seemingly become a standard of care for patients with neuropathy. Future investigations are needed to confirm the utility of these tests. In contrast, there is little consensus in regards to rheumatologic, immunologic, infectious, genetic, vitamin level testing, and skin and sural nerve biopsies. Most physicians indicate that these are not needed as part of the routine initial evaluation of patients with DSP, but there is still substantial utilization of these tests in the full work up. Future investigations are needed to clarify the role of these tests.

The most common cause of DSP is diabetes, and physicians clearly understand the need for testing for this condition. However, given that DSP and diabetes are each common conditions, the question remains concerning which tests to get for patients with both. In the scenario of patients with DSP and known diabetes, neurologists indicated that they would

order more SPEP and B12 tests than internists. As stated earlier, they also believe that EMGs are valuable in this patient population. Determining the appropriate evaluation in this population is important given that diabetes is by far the leading cause of DSP.^{4,6}

This study has important limitations. Our findings are based on self-report intent to order tests, not claims data. Thus we cannot account for actual physician action. However, the advantage of our study was the use of typical and standardized scenarios, which substantially reduces the potential confounding that can occur when assessing claims data for utilization in DSP. On the other hand, the limited clinical information in our survey scenarios may have not accounted adequately for the diverse presentations that occur in routine care. The brief scenarios also did not allow us to assess the effect of other important clinical aspects on test utilization. Our survey response rate was below 40%, which limits the generalizability of our findings. However, we did have a large number of responders, and importantly, responders and non-responders were similar in our available measures. The low number of neuromuscular physicians makes inferences about this physician group tenuous. We also investigated many comparisons without corrections. However, these results are meant to be hypothesis generating and many of our results revealed p values of <0.0001. Finally, despite the recent summary research on the value of tests in DSP, no current research uses optimal methodology to define the value of these tests by the impact of these tests on meaningful health outcomes.

Conclusion

We found significant variation in the evaluation of DSP, and the tests with the best evidence to support their use are often not ordered by physicians. GTTs are rarely ordered, particularly by internists, despite being one of the highest yield tests. This finding may be the result of the fact that there is controversy about whether IGT causes DSP^{14,16,18–20}. In contrast, MRI scans have significant utilization without a clear indication. More research is needed for physicians to be able to evaluate patients with DSP in an effective and efficient manner.

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Figure 1.

The percentage of tests indicated by provider type: A) in the initial evaluation of DSP (scenario 1); B) in the full evaluation of DSP (Scenario 1 plus 2)

Figure 2.

The percentage of AAN recommended tests (fasting glucose, SPEP, B12, GTT) indicated by provider type in the full evaluation of DSP

Table 1

Key demographics of responders and non-responders

	Responder N=429 Percent unless otherwise specified	Non-responder N=816 Percent unless otherwise specified	P value
Age (mean, SD)	47.4 (11.6)	48.3 (13.0)	0.22
Female gender	29.2	32.8	0.19
Specialty			<0.0001
Internist	40.1	52.3	
Neurologist	49.0	44.4	
Neuromuscular	11.0	3.3	
Degree			0.28
MD	94.6	96.0	
DO	5.4	4.0	
Years since graduation (mean, SD)	19.8 (12.1)	21.1 (13.1)	0.08
Region			0.05
1	24.3	29.9	
2	23.8	19.7	
3	29.7	32.1	
4	22.2	18.4	
MSA size			0.41
1	5.8	6.0	
4	0.2	1.0	
5	5.8	7.0	
6	88.1	86.1	
Fraction of neuropathy patients			
<1%	3.9		
1–5%	28.5		
6–10%	32.6		
11–20%	23.9		
21–50%	8.5		
>50%	2.7		
Practice Setting			
Private practice	43.7		
University	28.6		
Non-university teaching hospital	11.0		
Other	16.7		

Table 2

Number of tests by physician type under the following three clinical scenarios: initial evaluation of DSP, full evaluation of DSP, initial evaluation in a patient with diabetes (mean number of tests, (SD)).

Specialty	Initial*	Full*	Diabetes
Internist	10.6 (4.5)	14.5 (6.1)	6.5 (4.4)
Neurologist	12.2 (5.4)	17.5 (7.9)	6.6 (4.8)
Neuromuscular specialist	13.2 (5.4)	18.7 (6.4)	9.1 (5.6)

* Indicates that the t-test comparing internists to neurologists was statistically significant ($p < 0.01$)

Table 3

Fully adjusted models evaluating the association between key provider characteristics and number of all tests ordered (negative binomial) and those who ordered 3 or 4 AAN tests (logistic).

	# tests – OR (95% CI)	#AAN tests - OR (95% CI)
Age	1.00 (0.98–1.01)	0.99 (0.94–1.05)
Years since graduation	1.01 (0.99–1.02)	1.04 (0.98–1.10)
Gender (reference males)	1.05 (0.91–1.21)	1.01 (0.63–1.63)
MSA size (reference >250,000)	1.02 (0.84–1.23)	0.79 (0.41–1.51)
Region (reference Northeast)	Midwest: 1.01 (0.85–1.21)	Midwest: 1.25 (0.69–2.27)
	South: 0.99 (0.84–1.18)	South: 1.25 (0.71–2.23)
	West: 1.00 (0.83–1.20)	West: 1.17 (0.63–2.16)
Specialty (reference internists)	N: 1.17 (1.02–1.34)*	N: 1.73 (1.08–2.75)*
	NM: 1.31 (0.95–1.80)	NM: 5.46 (1.69–17.68)*
Degree (reference MD)	DO: 1.04 (0.80–1.37)	DO: 0.99 (0.39–2.49)
Practice setting (reference private practice)	University: 0.95(0.81–1.11)	University: 0.70 (0.41–1.19)
	Teaching hospital: 1.11 (0.90–1.36)	Teaching hospital: 1.51 (0.71–3.21)
	Other: 0.94 (0.79–1.12)	Other: 0.57 (0.32–1.04)
Frequency of neuropathy patients (reference 5% or less)	6–10%: 1.05 (0.91–1.23)	6–10%: 1.28 (0.77–2.15)
	11–20%: 1.04 (0.88–1.22)	11–20%: 0.99 (0.56–1.73)
	>20%: 0.99 (0.79–1.25)	>20%: 1.15 (0.54–2.45)

* Statistically significant, N=neurologist, NM=neuromuscular specialist