Does This Patient With Diabetes Have Large-Fiber Peripheral Neuropathy?

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Does This Patient With Diabetes Have Large-Fiber Peripheral Neuropathy?

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Context Diabetic peripheral neuropathy predisposes patients to foot ulceration that heals poorly and too often leads to amputation. Large-fiber peripheral neuropathy (LFPN), one common form of diabetic neuropathy, when detected early prompts aggressive measures to prevent progression to foot ulceration and its associated morbidity and mortality.

Objective To systematically review the literature to determine the clinical examination findings predictive of asymptomatic LFPN before foot ulceration develops.

Data Sources, Study Selection, and Data Extraction MEDLINE (January 1966–November 2009) and EMBASE (1980-2009 [week 50]) databases were searched for articles on bedside diagnosis of diabetic peripheral neuropathy. Included studies compared elements of history or physical examination with nerve conduction testing as the reference standard.

Data Synthesis Of 1388 articles, 9 on diagnostic accuracy and 3 on precision met inclusion criteria. The prevalence of diabetic LFPN ranged from 23% to 79%. A score greater than 4 on a symptom questionnaire developed by the Italian Society of Diabetology increases the likelihood of LFPN (likelihood ratio [LR], 4.0; 95% confidence interval [CI], 2.9-5.6; negative LR, 0.19; 95% CI, 0.10-0.38). The most useful examination findings were vibration perception with a 128-Hz tuning fork (LR range, 16-35) and pressure sensation with a 5.07 Semmes-Weinstein monofilament (LR range, 11-16). Normal results on vibration testing (LR range, 0.33-0.51) or monofilament (LR range, 0.09-0.54) make LFPN less likely. Combinations of signs did not perform better than these 2 individual findings.

Conclusions Physical examination is most useful in evaluating for LFPN in patients with diabetes. Abnormal results on monofilament testing and vibratory perception (alone or in combination with the appearance of the feet, ulceration, and ankle reflexes) are the most helpful signs.

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CLINICAL SCENARIOS

In the cases below, the clinician would like to know if the following patients with diabetes may have large-fiber peripheral neuropathy (LFPN).

Case 1

A 59-year-old woman with type 2 diabetes admits that she rarely checks her blood glucose level and is not careful with her diet. She denies any numbness or tingling in her feet, but on routine examination she cannot feel a Semmes-Weinstein monofilament.

Case 2

A 63-year-old man with a 7-year history of poorly controlled type 2 diabetes mellitus presents with numbness and paresthesias in his feet. He feels like he is walking on sand. On examination, decreased vibration sense at both ankles is found.

WHY IS THIS QUESTION IMPORTANT?

Peripheral neuropathy in patients with diabetes mellitus increases the risk of foot ulceration and diabetic foot infection 7-fold.[1-3] This, in turn, contributes to considerable morbidity and is the causative role in up to 61% of lower extremity amputations.[4] The mortality rate within 5 years after such amputation ranges from 39% to 80%.[5] Diabetes patients with predominantly LFPN tend to experience numbness and tingling in the feet, whereas those with small-fiber involvement describe sharp, burning, or shooting pain sensations.

Large-fiber peripheral neuropathy is often heralded by the insensate foot, though patients may be unaware of their condition. Nearly half of diabetes patients with foot ulceration lack symptoms of numbness or pain.[6,7] While most guidelines (http://guidelines.gov; search on "diabetic foot neuropathy") recommend annual inspection of the feet and monofilament testing for LFPN, some guidelines suggest options to use vibra-

See also Patient Page.

CME available online at www.jamaarchivescme.com and questions on p 1546.

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tion testing. The guidelines lack consistency on recommending a monofilament method, the number and location of sites that should be tested, or the number of abnormal responses that are considered positive for LFPN. One guideline reviews evidence that a single filament should not be used to test more than 10 patients in 1 session and that it should be left for at least 24 hours to recover its buckling strength between sessions.[8] Physicians who adhere to these monofilament recommendations could find that they need to screen a patient but have no suitable monofilament available. The objective of this review is to compare the test characteristics of patient questionnaires, symptoms, and bedside tests for evaluating LFPN in patients with diabetes to determine if a single test and method is both the most accurate and pragmatic.

CLINICIAL EVALUATION FOR DIABETIC LFPN

History

Patients with diabetes can develop neuropathies for reasons unrelated to diabetes. It is imperative that the clinician carry out a detailed medical history to help identify other conditions that may also cause or contribute to peripheral neuropathy. Some of these include alcoholism, vitamin B_{12} deficiency, endocrinopathies, vasculitides, heavy metal exposure, drug use, and malignancy (direct or paraneoplastic).[9] Further discussion regarding diagnosis, workup, and management of other etiologies of peripheral neuropathy is beyond the scope of this article and can be found in the referenced review.[9]

Large-fiber peripheral neuropathy in patients with diabetes is evaluated by inquiring about associated symptoms, letting the patient volunteer his/her symptoms before initiating systematic inquiry.[10] Microvascular complications such as erectile dysfunction, nephropathy, and retinopathy may predict the presence of peripheral neuropathy.[11]

Physical Examination

General Inspection. The presence of skin changes of the leg and foot, abnormal hair loss, and skin ulceration of the feet (including the heels and web spaces) should be noted.[12] The presence of a foot ulcer makes the likelihood of diabetic neuropathy extremely high.

Neurologic Examination. Examination for LFPN includes assessment of muscle strength, deep tendon reflexes, proprioception, vibration, and pressure sensation. Proprioception and evaluation of deep tendon reflexes and muscle strength is carried out per routine neurologic examination.

Vibration Sense Testing With a Tuning Fork. A 128-Hz tuning fork is activated by drawing together the prongs or tapping the fork forcefully against the palm of the hand to create vibrations. The force should not be loud enough to create audible humming. Before testing the feet, confirm that the patient perceives the vibration either on their sternum or hand.

An "on-off" technique to vibration testing is carried out by asking the patient to inform the examiner when the

Table 1. Characteristics of Primary Diagnostic Accuracy Studies

Source	Level of Evidence[12]	No. of Participants	No. (%)		Tests Evaluated	Patient Enrollment
			With Disease[a]	Asymptomatic[b]		
Beghi et al,[27] 1988	III	n = 48 (Type of diabetes not noted)	28 (58)	21 (44)	Components of physical examination Overall clinical examination Deep tendon reflexes Sensation Symptoms	Nonconsecutive (random sample)
Gentile et al,[28] 1995	IV	Type 1 diabetes: n = 6 Type 2 diabetes: n = 198	47 (23)	131 (64)	Symptom questionnaire Neurologic examination	Consecutive
Shin et al,[29] 2000	IV	n = 126 (Type of diabetes not noted)	67 (53)	9 (13)	SWMF	NA
Perkins et al,[11] 2001	III	Type 1 diabetes: n = 65 Type 2 diabetes: n = 361 Reference participants: n = 52	336 (79)[c] 8 (15)[d]	NA	SWMF Superficial pain Vibration (on-off) Vibration (timed)	Both[e]
Lee et al,[30] 2003	III	Type 2 diabetes: n = 37	29 (78)	13 (35)	SWMF	NA
Hsu et al,[31] 2005	IV	Type 2 diabetes: n = 112	30 (27)	NA	Neurological Symptom Score	NA
Moghtaderi et al,[32] 2006	I	Type 2 diabetes: n = 176	68 (39)	NA	Michigan Neuropathy Screening Instrument	Consecutive
Costa et al,[33] 2006	IV	Type 2 diabetes: n = 80 Controls: n = 45	60 (75)	35 (44)	Ability to walk on heels 5-Test Score	Consecutive
Papanas et al,[34] 2007	I	Type 2 diabetes: n = 120	92 (77)	NA	Neuropathy Disability Score	Consecutive

Abbreviations: NA, not available; SWMF, Semmes-Weinstein 5.07 monofilament.
[a] Based on nerve conduction testing.
[b] Based on clinical screening to enter study.
[c] Patients with diabetes.
[d] Reference participants.
[e] A combination of patients in a diabetes clinic referred to a neuropathy clinic, patients with unknown neuropathy status responding to a recruitment letter, and patients without diabetes.

Box. Questionnaire on Symptoms of Neuropathy (Italian Society of Diabetology)[28a]

1. Have you ever felt tingling, numbness, or heaviness in your hands or legs?
2. Have you ever felt burning, stabbing pain, pains, or cramps in your legs or arms?
3. Have you ever felt as if you were walking on foam or cotton wool or have you been unable to feel the unevenness (roughness) of the ground while walking?
4. Are you unable to feel the pain of burning or a cut?
5. Have you ever felt weakness in your legs while climbing or descending stairs?
6. Have you ever felt faint or dizzy on rising from bed?
7. Do you have difficulty in starting to urinate or loss of control of bladder function?
8. Do you have diarrhea, particularly in the night?
9. Have you ever sweat abundantly from your face only?
10. Do you have difficulty in maintaining an erection? (Men only)

[a] Each item is scored on a scale from 0 to 2: 0 = no, 1 = sometimes, and 2 = often. Questionnaire results considered positive when sum of scores of all questions is higher than 4 (must include a score of 2 for at least 1 of questions 3, 4, 9, or 10).

start and stop of the vibration is perceived on the bony prominence at the dorsum of the first toe. After the patient perceives the vibration, the examiner should dampen the tuning fork and the patient should report that the vibratory perception is gone. A "timed" technique is carried out by having the patient indicate when the vibrating sensation of the tuning fork starts and then stops. The examiner should immediately confirm the absence of vibration by placing the tuning fork on the dorsal bony prominence of his or her own thumb, though the examiner's perception of vibration for 10 or fewer seconds longer than the patient's is normal.[11] Duration of more than 10 seconds longer or asymmetry between the feet is abnormal.

Sensory Testing With the Semmes-Weinstein Monofilament. Semmes and Weinstein developed a series of 20 standardized monofilaments that buckle at forces ranging from 0.0045g to 447g.[13] Further evaluation of sensory thresholds in patients with leprosy and diabetes has suggested the 5.07 filament (which delivers a force of 10g to the skin when it buckles) as the testing threshold because patients perceiving this force tend not to have foot ulcers.[14]

With the patient supine and eyes closed, the monofilament is applied perpendicular to the skin of the foot until the filament buckles, holding the position for 1 second.[6,15] A number of sites should be tested in random order, avoiding ulcers, calluses, scars, or necrotic tissue. A normal result requires perception of the buckled monofilament at every site.

In terms of which sites to evaluate, the International Working Group on the Diabetic Foot evaluated 3 sites on each foot, requiring 2 of 3 to be insensate to represent diabetic peripheral neuropathy.[16] The US National Diabetes Education Program advises Semmes-Weinstein monofilament (SWMF) evaluation of 5 plantar sites on each foot: the great and fourth toes, and the first, third, and fifth metatarsal heads.[17]

METHODS

A structured search of MEDLINE (January 1966–November 2009) and EMBASE (1980-2009 [week 50]) was performed to retrieve relevant English-language articles on bedside diagnosis of diabetic peripheral neuropathy (eAppendix and eFigure [available at http://www.jama.com]).

Nerve conduction testing (NCT) is the most objective, sensitive, and reliable measure of large-fiber peripheral nerve function and has been used in large studies to evaluate screening tools for peripheral neuropathy.[18-23] It is the reference standard recommended by various consensus panels for the diagnosis of diabetic peripheral neuropathy. Use of nerve conduction testing as a reference standard also selects out patients with small-fiber peripheral neuropathy, which generally has normal test results.[24,25]

Prevalence, sensitivity, specificity, κ scores, likelihood ratios (LRs), and 95% confidence intervals (CIs) were calculated using conventional definitions.[26] Interrater agreement was assessed using κ statistics and their CIs, calculated in SAS software, version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Study Characteristics

Our search yielded 1388 articles, of which 9 on diagnostic accuracy[11,27-34] (TABLE 1) and 3 on precision[15,35,36] were included. Interrater agreement for selection and rating of articles on precision was good with unweighted κ = 0.44 (95% CI, 0.08-0.81) and weighted κ = 0.64 (95% CI, 0.29-1.00).

Prior Probability of LFPN

The prevalence of LFPN in the selected studies ranged from 23% to 79%. In the 2 studies with the highest quality (level of evidence I),[32,34] the prevalence was 39% to 77% (Table 1). All patients in the included studies had detailed histories and physical examinations to help exclude nondiabetes causes of peripheral neuropathy.

Accuracy of Symptoms for LFPN

From the 3 studies[27,28,31] evaluating various symptom question sets on history taking, only the questionnaire from the task force of the Italian Society of Diabetology[27,28] (BOX) was found to alter the likelihood of LFPN (score >4, LR, 4.0 [95% CI, 2.9-5.6]; score ≤4, LR, 0.19 [95% CI, 0.10-0.38]) (TABLE 2). In contrast, an abnormal result on the Neurological Symptom Score[31,37] or another question set posed by Beghi et al[27] did not modify the probability of disease (both had positive LRs of 1.0 and negative LRs of 0.9 and 1.0, respectively).

Accuracy of Physical Examination Maneuvers for LFPN

As the number of abnormal responses (with both the on-off and timed methods) on vibratory perception testing with a 128-Hz tuning fork increases, so does the likelihood of LFPN[11] (TABLE 3). For the on-off technique, Perkins et al[11] applied the fork twice to each foot, giving a score of 1 each time the tuning fork or its dampening were not felt (score range, 0-8). The timed technique was evaluated 4 times on each foot and considered abnormal if the physician perceived the vibration for more than 20 seconds longer than did the patient. Scores higher than 5 (on-off) or longer than 20 seconds (timed) greatly increased the likelihood of LFPN (LR, 35 and 16, respectively). Intermediate values of the on-off score also increased this LR (LR, 3.9; 95% CI, 2.0-7.5). Normal vibratory responses (scores of 0-1 or ≤10 seconds) make LFPN less likely (LR, 0.51 and 0.33, respectively).

Abnormal SWMF results increase the likelihood of LFPN (Table 3).[11,29,30] Despite differences in technique and threshold values, an abnormal test result had an LR in favor of the neuropathy in question (LR range, 11-16). Lee et al[30] considered test results abnormal if the patient could not perceive the SWMF at (1) either of 2 sites (third or

Table 2. Diagnostic Accuracy of Symptoms of Large-Fiber Peripheral Neuropathy in Patients With Diabetes

Source	Test	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Likelihood Ratio (95% CI)	
				Positive	Negative
Gentile et al, 1995[28]	Screening questionnaire[a]	85 (72-94)	79 (72-85)	4.0 (2.9-5.6)	0.19 (0.10-0.38)
Hsu et al, 2005[31]	Neurological Symptom Score	73 (54-87)	30 (21-42)	1.0 (0.81-1.4)	0.90 (0.46-1.7)
Beghi et al, 1988[27]	Any single symptom[b]	75 (55-89)	25 (9-49)	1.0 (0.72-1.4)	1.0 (0.37-2.7)

Abbreviation: CI, confidence interval.
[a] A score greater than 4 is a positive result (Box).
[b] Muscle cramps, burning feet, restless legs, muscle pain, trouble with object handling, impairment of standing and gait, or distal paresthesias.

Table 3. Diagnostic Accuracy of Physical Examination Maneuvers for Large-Fiber Peripheral Neuropathy in Patients With Diabetes

Maneuver by Source	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Likelihood Ratio (95% CI)	
			Positive	Negative
Individual components of clinical neurologic examination				
Vibration testing with 128-Hz tuning fork (Perkins et al,[11] 2001)				
On-off				
≥5 of 8[a]			35 (5.0-252)	
2-4 of 8			3.9 (2.0-7.5)	
≤1 of 8[b]			0.51 (0.45-0.57)	
Timed, per toe				
>20 seconds[c]			16 (5.3-51)	
11-20 seconds			1.1 (0.89-1.5)	
≤10 seconds[d]			0.33 (0.26-0.43)	
Semmes-Weinstein 5.07 monofilament				
Lee et al,[30] 2003	93 (77-99)	100 (63-100)	16 (1.1-244)	0.09 (0.03-0.29)
Shin et al,[29] 2000	57 (44-69)	95 (86-99)	11 (3.61-341)	0.46 (0.35-0.60)
Perkins et al,[11] 2001				
≥5 of 8[e]			11 (4.6-26)	
2-4 of 8			1.3 (0.94-1.7)	
≤1 of 8[f]			0.54 (0.46-0.64)	
Inability to walk on heels (Costa et al,[33] 2006)	25 (16-37)	98 (86-100)	11 (0.67-171)	0.76 (0.65-0.90)
Deep tendon reflexes (Beghi et al,[27] 1988)	71 (51-86)	80 (56-93)	3.6 (1.4-8.8)	0.36 (0.19-0.66)
Combinations of findings				
Neurologic examination (Gentile et al,[28] 1995)	94 (83-99)	92 (87-96)	12 (7.1-211)	0.07 (0.02-0.21)
Neuropathy Disability Score (Table 4) (Papanas et al,[34] 2007)[g]	85 (76-91)	82 (64-92)	4.7 (2.1-11)	0.19 (0.11-0.31)
5-Test Score ≥3 (Costa et al,[33] 2006)[h]	22 (12-33)	94 (68-99)	3.9 (0.25-60)	0.83 (0.68-1.0)
Michigan Neuropathy Screening Instrument, cut point ≥2 (Table 5) (Moghtaderi et al,[32] 2006)	65 (53-76)	83 (74-89)	3.8 (2.5-6.1)	0.42 (0.30-0.58)
Clinical examination (Beghi et al,[27] 1988)	75 (55-89)	70 (46-88)	2.5 (1.2-5.0)	0.83 (0.64-1.1)

Abbreviation: CI, confidence interval.
[a] Positive test result defined as 5 or more of 8 attempts insensate (diagnostic odds ratio, 48; 95% CI, 6.6-348).
[b] Negative test result defined as 1 or fewer of 8 attempts insensate (diagnostic odds ratio, 0.07; 95% CI, 0-0.10).
[c] Positive test result when vibration persists for longer than 20 seconds per toe (diagnostic odds ratio, 26; 95% CI, 8-82).
[d] Negative test result when vibration persists for 10 seconds or less per toe (diagnostic odds ratio, 0.17; 95% CI, 0.10-0.30).
[e] Positive test result defined as 5 or more of 8 attempts insensate (diagnostic odds ratio, 18; 95% CI, 7.1-44).
[f] Negative test result defined as 1 or fewer of 8 attempts insensate (diagnostic odds ratio, 0.14; 95% CI, 0.10-0.20).
[g] Abnormal score is 6 or higher.
[h] Valid once patients have tested negative for being unable to walk on their heels. The 5 tests are pain sensation (using a 25-×7-mm needle), vibration perception (128-Hz tuning fork), pressure sensation (Semmes-Weinstein 5.07 monofilament), ankle reflexes (sitting), and thermal sensitivity (cold spatula at 4°C).

Table 4. Neuropathy Disability Score[38]

Test	Site	Normal/Abnormal Result	Score[a]
Vibration perception threshold	128-Hz tuning fork at apex of great toe	Normal if can distinguish vibrating and not vibrating	Normal=0 Abnormal=1
Temperature perception	Dorsum of foot using tuning fork with beaker of ice/warm water	Normal if can distinguish cold object	Normal=0 Abnormal=1
Pinprick	Apply proximal to great toenail just enough to deform skin	Normal if can distinguish sharp and not sharp	Normal=0 Abnormal=1
Achilles reflex	Achilles tendon		Present=0 Present with reinforcement=1 Absent=2
Total score		Sum of 4 components; ≥6 is abnormal	

[a] Apply each test and score for each foot. Maximum total score is 8.

Table 5. Michigan Neuropathy Screening Instrument

Test	Score
Appearance of feet[a]	Normal=0 Abnormal=1
Ulceration	Absent=0 Present=1
Ankle reflexes	Present=0 Present with reinforcement=0.5 Absent=1
Vibration perception	Present=0 Reduced=0.5 Absent=1
Total score	Sum of 4 components; ≥2 is abnormal[b]

[a] Includes deformity, dry skin, callus, infection, and fissures.
[b] Maximum total score for each foot is 4 and for both feet is 8.

Table 6. Interobserver Reproducibility of History and Physical Examination Components for the Evaluation of Neuropathy in Patients With Diabetes

Findings	Reproducibility, κ
History[5a]	
Numbness	0.26
Dysthesias and paresthesias	0.57
Physical examination[b]	
Monofilament[6]	0.59
Ankle reflex[5,6c]	0.35-0.59
Position[5]	0.28
Vibration[5-7]	0.26-0.66
Clinical neuropathy[5a]	
2 Categories of neuropathy[d]	0.56
3 Categories of neuropathy[e]	0.33

[a] Indicates κ value of agreement between an internist and a neurologist.
[b] Studies include comparisons between internist and neurologist, internist and medicine resident or physician assistant, or unknown pairings.
[c] Two-category scale: present vs absent.
[d] No neuropathy or definite neuropathy.
[e] No neuropathy, possible neuropathy, or definite neuropathy.

fifth metatarsal heads) or (2) more than 4 of 10 sites.[30] This method had the highest positive likelihood (LR, 16; 95% CI, 1.1-244) but a favorable LR in ruling out the condition for negative testing (negative LR, 0.09; 95% CI, 0.03-0.29). Perkins et al[11] evaluated the SWMF similar to the on-off technique of vibratory perception. Shin et al[29] did not provide a description of their test points.

One study found that patients unable to walk on their heels had a high likelihood of LFPN, but the CI around the estimate was broad[33] (positive LR, 11; 95% CI, 0.67-171). Abnormal deep tendon reflexes increased the likelihood of LFPN in 1 study with narrower CIs than the heel walk test[27] (positive LR, 3.6; 95% CI, 1.4-8.8) (Table 3). This study described findings on reflexes only as "normal" or "impaired," with no details regarding which reflexes were evaluated. The presence of normal deep tendon reflexes and a normal heel walk were not efficient at identifying patients unaffected by LFPN.

Combinations of Findings for LFPN

A score higher than 3 on a numerically recorded neurologic examination evaluating knee and ankle reflexes, muscle trophism of lower limbs (dorsiflexor muscles of foot and big toe), muscle strength in lower limbs based on bilateral dorsiflexion against resistance, ability to walk on heels, and inspection of the foot had a high diagnostic accuracy for LFPN[28] (positive LR, 12; 95% CI, 7.1-211) (Table 3). Each item was scored on a scale of 0 to 2 (0 indicating normal and 2 indicating absent, severely impaired, or ulcerations). Normal evaluation in this study made neuropathy much less likely[28] (negative LR, 0.07; 95% CI, 0.02-0.21). This high diagnostic accuracy was not replicated by Beghi et al,[27] who evaluated a slightly different neurologic examination[27] (positive LR, 2.5; 95% CI, 1.2-5.0) compared with nerve conduction testing. In addition to sensation and deep tendon reflexes, the latter article evaluated strength, muscle tone, muscle bulk, and autonomic functions.[27,29]

Among patients able to walk on their heels, abnormal test results on 3 of 5 simple bedside tests (5-Test Score ≥3) had a positive LR of 3.9[33] (95% CI, 0.25-60) (Table 3) for LFPN. The 5-Test Score assesses pain sensation (using a 25-×7-mm needle), vibration perception (128-Hz tuning fork), pressure sensation (SWMF), ankle reflexes (sitting), and thermal sensitivity (cold spatula at 4°C).[33] However, both tests had low sensitivity (22%-25%), with wide 95% CIs, and, thus, require confirmation by larger studies.

Abnormal results on the Neuropathy Disability Score (TABLE 4)[38] and the Michigan Neuropathy Screening Instrument (TABLE 5) increased the likelihood of LFPN in 2 separate studies[32,34] (positive LRs of 4.7 [95% CI, 2.1-11] and 3.8 [95% CI, 2.5-6.1], respectively) (Table 3). In the Michigan Neuropathy Screening Instrument, vibration perception was recorded as "re-

duced" when the patient could not sense the tuning fork on the fingernails but could sense it on the lateral malleolus. Similarly, the vibration component was considered "absent" when felt by the examiner but not the patient. Although these 2 scores that combined multiple signs were accurate, neither performed better than the individual findings of vibration testing or monofilament.

Precision of Signs and Symptoms

Eliciting symptoms of LFPN on history taking had, at best, fair to moderate overall precision (κ=0.26-0.57),[35] with "paresthesias" having the best interobserver agreement (TABLE 6). All physical examination maneuvers in these studies had similar precision (κ=0.26-0.59), with vibration testing, ankle jerk, and monofilament testing having the best reproducibility.[15,35,36] The vibration testing method used by O'Neill et al[36] was the on-off technique, whereas Smieja et al[15] used a timed method with a cutoff of 5 seconds. Overall, internists were more apt to diagnose a patient as having clinical neuropathy than were neurologists (37% vs 25%).[35]

LIMITATIONS OF THE LITERATURE

There are several important limitations to consider when interpreting the included studies. First, there is a paucity of data in the literature on this topic. Many of the studies that do exist have small numbers of patients and evaluate numerous tests at any given time, not always with recommended criterion standards. Our inclusion criteria were quite stringent; as such, we included only 9 studies (2 of high quality) in this review. It is assumed that the operating characteristics presented in Table 2 and Table 3 are for LFPN, as they are calculated against a gold standard that is generally negative in the setting of small-fiber peripheral neuropathy. However, to ensure that we captured all articles evaluating maneuvers for LFPN, studies that evaluated components of small-fiber peripheral neuropathy (in addition to LFPN) were also included. The various techniques used for specific maneuvers also varied between studies. The 3 studies evaluating the SWMF used different protocols and sites on the feet. Thus, we cannot say with certainty if one technique results in improved detection of LFPN over another.

SCENARIO RESOLUTION

Case 1

This woman with type 2 diabetes and probable macrovascular complications is asymptomatic with regard to peripheral neuropathy. The pretest probability of LFPN ranges from 40% to 70% based on level I studies included in this review. The LR for abnormal SWMF testing is as high as 16. Therefore, her posttest probability is higher than 95%.

Case 2

This is a man with symptoms of peripheral neuropathy and poorly controlled diabetes. His symptoms are those of LFPN (vs small-fiber peripheral neuropathy, which is classically described as painful). Absence of vibratory perception using a tuning fork indicates that his likelihood of LFPN is quite high (LR, 16-35).

CLINICAL BOTTOM LINE

Diagnosing LFPN in patients with diabetes requires the combination of a thorough patient history (often to rule out other potential causes of neuropathy) and physical examination. The presence or absence of neuropathic symptoms is less useful than the physical findings for LFPN. However, symptoms in the absence of signs can indicate the presence of small-fiber neuropathy. A clinical examination combining evaluation for vibration perception, ankle reflexes, ulceration, and overall appearance of the feet is more helpful than any of these symptoms alone. The use of a monofilament and a tuning fork should be standardized to recommended methods. One systematic review also found evidence that use of a single monofilament has limitations in the number of patients on which it can be used, and that it requires a "rest" to regain its buckling strength. Failure of a patient to detect vibration perception with a 128-Hz tuning fork or a 5.07 SWMF are the best predictors of LFPN and work better than combinations of signs.

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Study concept and design: Kanji, Anglin, Hunt, Panju.
Acquisition of data: Kanji, Anglin, Hunt.
Analysis and interpretation of data: Kanji, Hunt, Panju.
Drafting of the manuscript: Kanji, Anglin, Hunt, Panju.
Critical revision of the manuscript for important intellectual content: Hunt, Panju.
Statistical analysis: Kanji.
Administrative, technical, or material support: Panju.
Study supervision: Hunt, Panju.
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Online-Only Material: The eAppendix and eFigure are available at http://www.jama.com.
Additional Contributions: David Edelman, MD, Richard Bedlack, MD, PhD, and Matt Crowley, MD, Duke University, reviewed an early version of the manuscript and provided input and comments. They did not receive compensation. Joanne Gunby, RN, McMaster University, assisted with editing of multiple versions of the manuscript and received compensation for her work.

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