

Sensitivity and specificity of a new indicator test (Neuropad) for the diagnosis of peripheral neuropathy in type 2 diabetes patients: a comparison with clinical examination and nerve conduction study

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Abstract

Objective: The objective of this study was to evaluate the sensitivity and specificity of a new indicator test (Neuropad) for the diagnosis of peripheral neuropathy in type 2 diabetes patients as compared with clinical examination and nerve conduction study (NCS). **Patients and Methods:** This study included 120 type 2 diabetes patients (58 men) with a mean age of 67.3 ± 5.9 years and a mean diabetes duration of 13.1 ± 3.2 years. Diabetic neuropathy was diagnosed through the Neuropathy Disability Score. An NCS was performed on radial, ulnar, sural, and common and deep peroneal nerves. Patients were also examined with the new indicator test. The “time to complete color change of the test” from blue to pink was recorded. The test was considered abnormal in patients who exhibited a time to complete color change of the test exceeding 600 s in at least one foot. **Results:** Neuropathy was diagnosed by clinical examination in 83 (69.2%) patients. The sensitivity of the indicator test for clinical neuropathy was 95.2%, and its specificity was 67.6%. The sensitivity of NCS for clinical neuropathy was 94%, and its specificity was 62.1%. The sensitivity of the indicator test for abnormal NCS was 97.8%, and its specificity was 96.4%. **Conclusions:** The new indicator test has a very high sensitivity not only for the diagnosis of clinical neuropathy but also for the diagnosis of neurophysiological neuropathy. Specificity is moderately high for the diagnosis of clinical neuropathy, while it is particularly high for the diagnosis of neurophysiological neuropathy. The indicator test has a validity comparable to that of NCS for the diagnosis of diabetic neuropathy. Finally, the time to complete color change of the test is associated with the severity of nerve conduction impairment.

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1. Introduction

Foot ulceration and amputation are two of the most common chronic complications of diabetes mellitus that have a considerable adverse impact on morbidity (Boulton,

Vileikyte, Ragnarson-Tennvall, & Apelqist, 2005; Jeffcoate & Bakker, 2005). Neuropathy is of crucial importance in the pathogenesis of foot ulcers (Boulton, 2004; Reiber et al., 1999). In everyday practice, clinical examination is the mainstay for the diagnosis of neuropathy (Boulton, 2004; Boulton, Vileikyte, et al., 2005; Valk, Nauta, Stijers, & Bertelsmann, 1992). A nerve conduction study (NCS) significantly contributes to the diagnosis of neuropathy, enabling an early diagnosis of nerve injury (Krarup, 2003; Olaleye, Perkins & Bril, 2001; Rota et al., 2005). Nonethe-

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less, it is not generally available and cannot, therefore, be widely used as a screening test (Boulton, 2004; Boulton, Vinik, et al., 2005).

More recently, a new indicator test (Neuropad) that measures sweat production has been proposed as a new test of neuropathy (Manes et al., 2004; Marinou et al., 2005; Papanas, Papatheodorou, Christakidis, et al., 2005; Zick, Schäper, & Deeters, 2003). Interestingly, the indicator test enables the diagnosis of neuropathy in a substantial proportion of patients with normal clinical examination (Papanas, Papatheodorou, Christakidis, et al., 2005). Previous work from our group has also shown an association between the indicator test and the clinical severity of neuropathy (Papanas, Papatheodorou, Christakidis, et al., 2005). More importantly, an excellent reproducibility of the test has been reported (Papanas, Papatheodorou, Papazoglou, et al., 2005).

However, no study has so far examined the validity of the indicator test as compared with that of NCS. Therefore, the aim of the present study was to evaluate the sensitivity and specificity of the new indicator test (Neuropad) for the diagnosis of peripheral neuropathy in type 2 diabetes patients in comparison with those of clinical examination and NCS.

2. Patients and methods

This study included 120 patients (58 men and 62 women) with type 2 diabetes mellitus. The mean age was 67.3 ± 5.9 years and the mean diabetes duration was 13.1 ± 3.2 years. Patients were recruited from the Outpatient Department of Obesity, Diabetes, and Metabolism of the Second Department of Internal Medicine at the Democritus University of Thrace and from the Diabetic Department of the General Hospital of Alexandroupolis. Recruitment was consecutive and performed in a tertiary care setting. The control group comprised 30 healthy volunteers (15 men; mean age, 63.8 ± 4.6 years). The study was approved by the institutional ethics committee, and all patients gave their informed consent.

The exclusion criteria were as follows: peripheral arterial occlusive disease, chronic alcohol abuse, thyroid disease, vitamin B₁₂ depletion, lumbar spine disorders, or any other cause of peripheral neuropathy.

Diabetic neuropathy was diagnosed through the Neuropathy Disability Score (NDS) (Young, Boulton, MacLeod, Williams, Sonksen, 1993). This is a standardized examination of ankle reflexes; this also includes tuning fork (128 Hz), pinprick, and cold tuning fork (temperature sensation) at the hallux, as described earlier (Young et al., 1993). Sensory modalities (by tuning fork, pinprick, and cold tuning fork) were scored as follows: 0=*present* and 1=*reduced/absent* on each side (Young et al., 1993). Reflexes were scored as follows: 0=*normal*, 1=*present with reinforcement*, and 2=*absent* on each side (Young et al., 1993). Clinical

neuropathy was defined as an NDS of ≥ 6 (Paisley, Abbott, van Schie, & Boulton, 2002; Young et al., 1993).

Examination with the new indicator test (Neuropad) was performed as follows (Papanas, Papatheodorou, Christakidis, et al., 2005; Zick et al., 2003). Patients were allowed to rest at constant room temperature (25°C) for 10 min after they had taken off their socks and shoes. Indicator tests were applied to a callus-free area on the plantar surface of the feet at the level of the first to the second metatarsal heads bilaterally. The “time to complete color change of the test” from blue to pink was recorded (Papanas, Papatheodorou, Christakidis, et al., 2005). The complete color change of the test in both feet within 600 s was considered a normal response. The test was considered abnormal in patients who exhibited a time to complete color change of the test exceeding 600 s in at least one foot (Papanas, Papatheodorou, Christakidis, et al., 2005; Zick et al., 2003).

An NCS comprising conduction velocities, latencies, and action potential amplitudes was carried out with a Nihon Kohden Neuropack Four Mini using temperature control and fixed distance for motor conduction. The motor conduction of the radial, ulnar, and common and deep peroneal nerves, as well as the sensory conduction of the radial, ulnar, and sural nerves, was recorded in non-dominant limbs. Motor conduction was studied at the radial nerve by recording at the extensor digitorum communis and by stimulation: (a) 6 cm centrally; (b) between the brachioradialis and the tendon of biceps; and (c) between the coracobrachialis and the medial edge of the triceps. Motor conduction was studied at the ulnar nerve by recording at the abductor digiti minimi and by stimulation: (a) 8 cm centrally at the wrist; (b) below the elbow; and (c) above the elbow. Motor conduction was assessed at the common and deep peroneal nerves by recording at the extensor digitorum brevis and by stimulation: (a) 7 cm centrally; (b) below the head of the fibula; and (c) above the head of the fibula. Motor conduction in the aforementioned nerves was studied both centrally and distally in order to exclude entrapment neuropathies. After the exclusion of these conditions, distal motor nerve conduction was used for the assessment of diabetic neuropathy (Feldman et al., 1994; Olaleye et al., 2001). Sensory conduction was studied at the radial nerve by antidromic stimulation at the lateral edge of the radius in the distal forearm and by recording at the back of the hand between the first and the second metacarpals. Sensory conduction was studied at the ulnar nerve by orthodromic stimulation at the fifth digit and by recording at the wrist. Sensory conduction was studied at the sural nerve by antidromic stimulation along the posterior surface of the distal leg and by recording behind the lateral malleolus.

All conduction velocities and action potential amplitudes were scored as 0=*normal* and 1=*abnormal*. The normal range used was the mean reference value ± 2 S.D.; measurements outside these values are classified as abnor-

Table 1
Examination with Neuropad and NCS in diabetic patients with or without neuropathy

Clinical neuropathy status			
	With clinical neuropathy (n=83) [n (%)]	Without clinical neuropathy (n=37) [n (%)]	P ^a
Abnormal Neuropad	79 (95.2)	12 (32.4)	.001
Normal Neuropad	4 (4.8)	25 (67.6)	
Abnormal NCS	78 (94)	14 (37.8)	.001
Normal NCS	5 (6)	23 (62.2)	
Confirmed clinical neuropathy status			
	With confirmed clinical neuropathy (n=78) [n (%)]	Without confirmed clinical neuropathy (n=42) [n (%)]	P ^a
Abnormal Neuropad	78 (100)	13 (31)	.001
Normal Neuropad	0 (0)	29 (69)	

^a Patients with neuropathy versus patients without neuropathy.

mal. The aforementioned normal reference values were obtained by an examination of age-matched subjects from the population of the same area. The sum of abnormal scores was used to define the total NCS score (range, 0–14). Neuropathy was defined as a total NCS score of ≥ 3 (Olaleye et al., 2001). Nerve conduction impairment was considered moderate in patients with an NCS score of 3–5 and severe in those with an NCS score of ≥ 6 . Patients with nerve conduction impairment in whom the number of abnormal sensory nerve attributes was higher than the number of abnormal motor nerve attributes were considered

to have primary sensory nerve conduction impairment. Conversely, those in whom the number of abnormal motor nerve attributes was higher than the number of abnormal sensory nerve attributes were considered to have primary motor nerve conduction impairment. The concurrence of both abnormal clinical examination and NCS impairment was defined as confirmed clinical neuropathy (The Diabetes Control and Complications Trial Research Group, 1995). Each diagnostic test (clinical examination, examination with Neuropad, and NCS) was conducted by an operator who was blinded to the results of the other tests.

Statistical analysis was performed using the Statistical Package for Social Sciences, version 11.0. The significance of qualitative variables was assessed by chi-square test (with Yates' correction for 2x2 contingency tables). Normally distributed quantitative variables were analyzed by analysis of variance and unpaired *t* test. Data were expressed as mean \pm 1 S.D. ($x \pm 1$ S.D.). Significance was defined at 5% level ($P < .05$).

3. Results

Neuropathy was diagnosed by clinical examination in 83 (40 men and 43 women; 69.2%) patients. Abnormal Neuropad examination was observed in 79 (95.2%) patients with clinical neuropathy and in 12 (32.4%) patients without clinical neuropathy (Table 1). The sensitivity of the indicator test for neuropathy was 95.2%, and its specificity was 67.6%. The positive prognostic value was 86.8%, and the negative prognostic value was 86.2%.

Table 2
Time to color change of the indicator test in relation to neuropathy status and NCS in patients and healthy controls

Time to color change in relation to clinical neuropathy status** (s) (mean \pm S.D.)			
Patients with clinical neuropathy	Patients without clinical neuropathy	Healthy controls	Statistical evaluation
1450 \pm 320	462 \pm 70	242 \pm 36	Patients with vs. patients without clinical neuropathy: $P = .002$ Patients with clinical neuropathy vs. controls: $P = .001$ Patients without clinical neuropathy vs. controls: $P = .01$
Time to color change in relation to confirmed clinical neuropathy status** (s) (mean \pm S.D.)			
Patients with confirmed clinical neuropathy	Patients without confirmed clinical neuropathy	Healthy controls	Statistical evaluation
1570 \pm 380	481 \pm 80	242 \pm 36	Patients with vs. patients without confirmed clinical neuropathy: $P = .001$ Patients with confirmed clinical neuropathy vs. controls: $P = .001$ Patients without confirmed clinical neuropathy vs. controls: $P = .01$
Time to color change in relation to NCS* (s) (mean \pm S.D.)			
Patients with normal NCS	Patients with abnormal NCS	Healthy controls	Statistical evaluation
1830 \pm 328	490 \pm 85	242 \pm 36	Patients with normal vs. patients with abnormal NCS: $P = .001$ Patients with abnormal NCS vs. controls: $P = .001$ Patients with normal NCS vs. controls: $P = .02$

* Significant difference between groups ($P = .002$).

** Significant difference between groups ($P = .001$).

An abnormal NCS was observed in 78 (94%) patients with clinical neuropathy and in 14 (37.8%) patients without clinical neuropathy (Table 1). The sensitivity of NCS for clinical neuropathy was 94%, and its specificity was 62.1%. The positive and negative prognostic values were 84.8% and 82.1%, respectively.

Neuropad examination was abnormal in 90 (97.8%) patients with abnormal NCS and in 1 (1.1%) patient with normal NCS ($P=.001$). The sensitivity of the indicator test for abnormal NCS was 97.8%, and its specificity was 96.4%. The positive prognostic value was 98.9%, and the negative prognostic value was 93.1%.

Among patients with abnormal NCS ($n=92$), nerve conduction impairment was primarily sensory in 62 patients and primarily motor in 30 patients. Neuropad examination was abnormal in 61 (98.4%) patients with the former and in 29 (96.7%) patients with the latter. There was no difference ($P=NS$) in sudomotor impairment between these two conditions, as assessed by Neuropad.

Confirmed clinical neuropathy was diagnosed in 78 (37 men and 41 women; 65%) patients. Abnormal Neuropad examination was observed in 78 (100%) patients with confirmed clinical neuropathy and in 13 (31%) patients without confirmed clinical neuropathy (Table 1). The sensitivity of Neuropad for confirmed clinical neuropathy was 100%, and its specificity was 69%. The positive prognostic value was 85.7%, and the negative prognostic value was 100%.

The time to color change of the indicator test in patients according to their neuropathy status (with and without clinical neuropathy, with and without confirmed clinical neuropathy), in patients according to NCS findings (normal or abnormal NCS), and in healthy controls is shown in Table 2. Differences were significant between the groups, as summarized in the same table.

In patients with clinical neuropathy, Neuropad examination was abnormal in 38 of 40 men and in 41 of 43 women. The sensitivity was 95% in men and 95.3% in women. The specificity was 66.7% in men and 68.4% in women. The positive prognostic value was 86.4% in men and 87.2% in women. The negative prognostic value was 85.7% in men and 86.7% in women. In patients with confirmed clinical neuropathy, Neuropad examination was abnormal in 37 of 37 men and in 41 of 41 women. The sensitivity was 100% both in men and in women. The specificity was 71.4% in men and 66.7% in women. The positive prognostic value was 86% in men and 85.4% in women. The negative prognostic value was 100% both in men and in women.

Among patients with an abnormal NCS, a further significant difference ($P=.01$) was demonstrated in time to complete color change of the test in relation to the severity of nerve conduction impairment. Indeed, this time was significantly higher in patients with severe nerve conduction impairment (892 ± 179 s) than in those with moderate nerve conduction impairment (1983 ± 386 s).

4. Discussion

The present study showed that the new indicator test has a very high sensitivity (95.2%) for the diagnosis of neuropathy, while its specificity is less (67.6%). These results are in agreement with those of previous studies (Marinou et al., 2005; Papanas, Papatheodorou, Christakidis, et al., 2005; Zick et al., 2003). It has been proposed that the specificity of the indicator test cannot be higher since the test permits the diagnosis of neuropathy in a considerable proportion of patients with normal clinical findings (Papanas, Papatheodorou, Christakidis, et al., 2005). This was also the case in the present study, with neuropathy being diagnosed by the indicator test in 32.4% of patients without clinical evidence of neuropathy. The ability of the test to diagnose neuropathy even in patients with normal clinical findings has been attributed to the fact that the test assesses sudomotor function (Papanas, Papatheodorou, Christakidis, et al., 2005). Indeed, there is evidence to suggest that sudomotor dysfunction may develop early in diabetes and can thus be detected even in patients with normal clinical examination (Braune & Horter, 1996; Caccia et al., 1991; Hoeldtke et al., 2001; Kennedy & Navarro, 1989; Shimada et al., 2001). Given that sudomotor dysfunction has been shown to be mediated by small-fiber injury (Abdel-Rahman, Collins, Cowen, & Rustin, 1992; Low, 2004), this argument is reinforced by recent pathological studies that have been able to show that small-fiber injury may occur early in diabetic patients with normal clinical examination (Malik et al., 2005) or even earlier in patients with impaired glucose tolerance (Sumner, Sheth, Griffin, Cornblath, & Polydefkis, 2003).

NCS also enabled the diagnosis of neuropathy in 37.8% of patients without clinical signs. This is not unexpected since NCS permits an early diagnosis of subclinical neuropathy (Krarup, 2003; Olaleye et al., 2001; Rota et al., 2005). Consequently, NCS had a specificity of 62.1% for the diagnosis of clinical neuropathy, similar to the indicator test. As anticipated, the sensitivity of NCS for the diagnosis of clinical neuropathy was very high, in keeping with the findings of Valk et al. (1992). Interestingly, the sensitivity, specificity, and prognostic values of NCS were comparable with those of Neuropad.

Abnormal Neuropad examinations were significantly more frequent in patients with nerve conduction impairment than in those with normal neurophysiological examination. More importantly, it was demonstrated that both the sensitivity and the specificity of the indicator test for abnormal NCS were particularly high (97.8% and 96.4%, respectively). Although the indicator test evaluates sudomotor function (Manes et al., 2004; Papanas, Papatheodorou, Christakidis, et al., 2005; Zick et al., 2003) and NCS is a measure of large fiber function (Krarup, 2003; Olaleye et al., 2001), the indicator test managed to identify all but two patients with abnormal NCS score. Arguably, this may be explained by the fact that diabetic

neuropathy involves both small and large fibers (Duby, Cambell, Setter, White, & Rasmussen, 2004; Sima, 2003). Of note, the sensitivity and the specificity of Neuropad for NCS were higher than those for clinical neuropathy. This may be ascribed to the fact that both Neuropad and NCS are more objective than clinical examination, which requires patient cooperation. From a practical point of view, the indicator test had a validity comparable to that of NCS for the diagnosis of diabetic neuropathy. It is, therefore, plausible that an inquiry into the utility of the indicator test in the detection of subclinical neuropathy is warranted. Additionally, it would be interesting to investigate whether the indicator test enables an assessment of the risk for developing foot complications, as has been shown for NCS (Carrington et al., 2002).

As might be expected, the majority of patients (67.4%) with abnormal NCS had primary sensory nerve impairment (Pastore, Izura, Geijo-Barrientos, & Domingues, 1999; Rota et al., 2005; Valk et al., 1992). There was no difference in abnormal Neuropad examination between primary sensory nerve impairment and primary motor nerve impairment. This may be attributable to the very high frequency of abnormal Neuropad examination in patients with impaired NCS. Indeed, abnormal Neuropad examination was very frequent both in patients with sensory nerve involvement (98.4%) and in those with motor nerve involvement (96.7%). In practice, it appears that the indicator test is not helpful in differentiating between primary sensory nerve involvement and primary motor nerve involvement.

Furthermore, the combination of clinical examination and NCS was used to provide a more robust diagnosis of neuropathy, in accordance with the San Antonio consensus statement that a diagnosis of neuropathy should incorporate various diagnostic tests (American Diabetes Association & American Academy of Neurology, 1988). The concurrence of abnormal clinical examination and NCS impairment was defined as confirmed clinical neuropathy, a term borrowed from the The Diabetes Control and Complications Trial Research Group (1995). Neuropad showed a particularly high sensitivity (100%) for confirmed clinical neuropathy, while its specificity was similar to that for clinical neuropathy. These findings confirm the validity of the indicator test in the diagnosis of neuropathy.

Analysis according to gender showed that the sensitivity and the specificity of the indicator test for clinical neuropathy were similar in men and in women. This was also the case for confirmed clinical neuropathy. Consequently, no difference was identified between men and women in the diagnostic validity of the indicator test. This new finding suggests that the indicator test is independent of potential minor skin differences between males and females, and enhances its utility as a diagnostic modality.

The time to complete color change of the test was significantly higher in patients with clinical neuropathy than in those without clinical neuropathy. This result is in accordance with previous findings (Papanas, Papatheodorou,

Christakidis, et al., 2005; Zick et al., 2003). The same difference was also observed between patients with and patients without confirmed clinical neuropathy. Moreover, it was found that the time to complete color change of the test was significantly higher in patients with abnormal NCS than in those with normal NCS. Hence, a prolonged time to complete color change of the test is associated with the diagnosis of not only clinical neuropathy but also neurophysiological neuropathy.

We have previously reported a significant association between the time to complete color change of the test and the severity of clinical neuropathy (Papanas, Papatheodorou, Christakidis, et al., 2005). The present investigation extended this association to the severity of nerve conduction impairment. The time to color change was significantly longer in patients with severe nerve conduction impairment than in those with moderate nerve conduction impairment. Accordingly, the time to complete color change of the test was an index of the severity of nerve conduction impairment.

The implications of our findings for clinical practice are as follows. The indicator test may be used as a highly sensitive tool for the diagnosis of both clinical neuropathy and neurophysiological neuropathy. It should be noted that the indicator test has a validity comparable to that of NCS for the diagnosis of diabetic neuropathy. However, NCS is not universally available, in contrast to the indicator test, which is a widely applicable, reproducible, and easy-to-use diagnostic tool (Papanas, Papatheodorou, Christakidis, et al., 2005; Papanas, Papatheodorou, Papazoglou, et al., 2005). These findings imply a potential role for the indicator test in increasing the sensitivity for the diagnosis of neuropathy in the vulnerable diabetic population. In this respect, the sensitivity and the high reproducibility of the test satisfy the recommendations for a diagnostic procedure formulated as early as the composition of the San Antonio consensus statement (American Diabetes Association & American Academy of Neurology, 1988). However, there is no evidence that the indicator test may replace the validated NCS, and further research is warranted before the encouraging results of the present study are applied to the general diabetic population.

In conclusion, the new indicator test has a very high sensitivity for the diagnosis of not only clinical neuropathy but also neurophysiological neuropathy. Specificity is moderately high for the diagnosis of clinical neuropathy, while it is particularly high for the diagnosis of neurophysiological neuropathy. Moreover, the indicator test has a validity comparable to that of NCS for the diagnosis of diabetic neuropathy. Finally, the time to complete color change of the test is associated with the severity of nerve conduction impairment. These results provide further evidence for the clinical utility of the indicator test in the timely diagnosis of neuropathy. Therefore, the new test may prove to be of value in the detection of patients at high risk for foot complications.

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