Skin wrinkling for diagnosing small fibre neuropathy: comparison with epidermal nerve density and sympathetic skin response

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ABSTRACT

Objective: To compare simple tests of small nerve fibre function with intraepidermal nerve fibre density (IENFD) in the evaluation of small fibre neuropathy (SFN).

Methods: Patients with idiopathic SFN of the hands were prospectively studied. Evaluation involved clinical examination, nerve conduction studies, sympathetic skin response (SSR) and skin wrinkling stimulated by water and EMLA (eutectic mixture of local anaesthetics).

Results: Of 21 patients, 16 (76%) had low IENFD, 15 (71%) impaired water-induced wrinkling, 14 (67%) impaired EMLA-induced wrinkling, and nine (43%) abnormal SSR.

Conclusions: Stimulated skin wrinkling was nearly as sensitive as IENFD in diagnosing SFN, whereas SSR was of less use. Stimulated skin wrinkling is a useful supportive test when IENFD or other tests of small nerve fibre function are not available.

Establishing a diagnosis of small fibre neuropathy (SFN) can be challenging because of the special diagnostic tests required for confirmation.[1] The clinical syndrome is characterised by numbness or paraesthesias, which are painful burning or tingling in the absence of significant large nerve fibre abnormality.[1] Investigations aim to identify causes while confirming small nerve fibre abnormality. Causes are found in 20–50% of cases and include diabetes mellitus, abnormal glucose metabolism and paraproteinaemias.[2 3]

Patients with SFN undergo a battery of testing when these are available. The most common test, sympathetic skin response (SSR), has varying sensitivity and repeatability because of its complex peripheral and central pathways.[1 4] Other tests include quantitative sudomotor axonal reflex testing (QSART), quantitative sensory testing, cardiovagal and autonomic tests based on blood pressure, vasomotor reflex testing and intraepidermal nerve density (IENFD). Although comparisons between functional modalities (QSART, quantitative sensory testing, SSR, cardioautonomic testing) and IENFD in diagnosing SFN are few, there is evidence that IENFD is one of the more sensitive and reliable tests.[3] It is therefore incorporated into guidelines for diagnosing and quantifying SFN.[5]

However, IEFND is limited by cost, by not providing information on function, its inconvenience and discomfort, and lengthy processing and reporting time.

Stimulated skin wrinkling (SSW), induced by water or a eutectic mixture of local anaesthetics (EMLA), is another test of small nerve fibre function.[6 7] The mechanism of this test of limb sympathetic dysfunction has recently been elucidated.[8 9] Wrinkling, which occurs in glabrous hand and to a lesser degree in foot skin, results from vasoconstriction controlled by sympathetic fibres.[8] It has been used to establish SFN in diabetes and leprosy.[10 11]

Except for SSR, tests of small nerve fibre function involve specialised equipment and expertise which few facilities apart from tertiary centres have. There is need for a simple, economical test of small fibre abnormality. We studied the potential role of SSW in the assessment of SFN by comparing it with IEFND and SSR.

MATERIALS AND METHODS

Data presented here were taken from a prospective study investigating the diagnostic sensitivities of SSR and IENFD in patients with sensory neuropathy. From 2001 to 2003, patients were investigated at the National University Hospital, Neuroscience Clinic, Singapore, a referral centre serving a population of 1 million. The hospital ethics board reviewed and approved the study.

Patients

After giving consent, 69 patients with foot and hand dysaesthesia were recruited. To test as homogeneous a group of neuropathies as possible, we excluded patients with a discernible cause of neuropathy and evidence of large fibre neuropathy. Exclusion criteria were: cancer, chemotherapy, alcohol abuse, solvent exposure, dementia, spinal cord and root disease or significant limb trauma, abnormality of fasting blood sugar, thyroid dysfunction (thyrotropin releasing hormone and thyroxine) paraproteinaemias (protein immunoelectrophoresis), connective tissue disease (C reactive protein, C3/C4 complement, antibodies to double-stranded DNA, rheumatoid factor), abnormal tendon reflexes, superficial touch, sharp pain, vibration and proprioception and abnormal nerve conduction studies (bilateral median, ulnar, tibial, peroneal and sural nerves). A neurologist performed the examination. Nerve conduction studies, SSR, IENFD and SSW were performed within a week of clinical examinations.

Tests of nerve function

Motor and sensory nerve conduction and SSR of four limbs were performed unblinded to clinical status, using two-channel electromyography (Medlec Synergy, Oxford Instruments, Oxford, UK) with standard settings and procedures.[12 13]

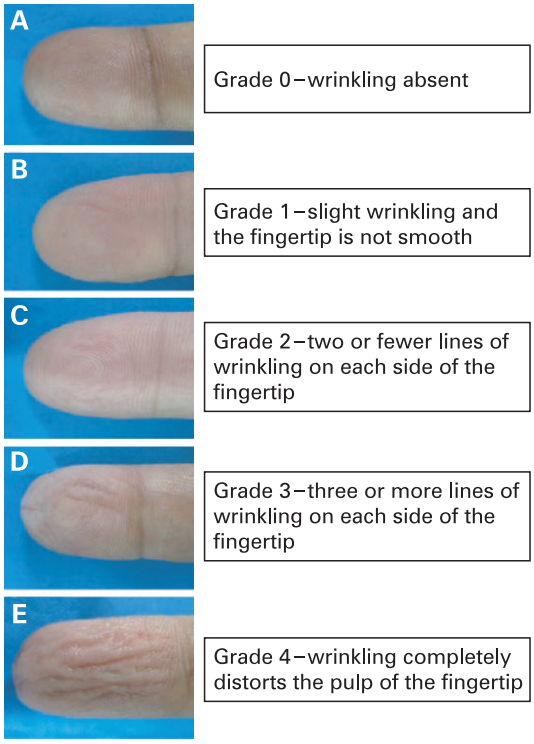

Figure 1 Stimulated wrinkling grading.

For water-induced skin wrinkling, the subject's right hand was immersed in 0.5 mmol/l NaCl solution for 30 min at 40°C.[14] For EMLA-induced wrinkling, the distal digit pulp of the left 3rd, 4th and 5th fingers was covered with EMLA cream for 30 min.[7] Aqueous cream over the 2nd digit was the control.

Skin wrinkling was graded using a published scale (fig 1A–E).[11] EMLA wrinkling grades for digits 3, 4 and 5 were totalled and averaged. Water wrinkling grades for digits 2, 3, 4 and 5 were totalled and averaged. Skin wrinkling was abnormal if the averaged score showed absence or severe impairment of wrinkling (grade 0–2). Wrinkling grades were: 0, wrinkling absent; 1, just perceptible wrinkling, fingertip not smooth; 2, two or fewer lines of superficial wrinkling; 3, three or more lines of deep wrinkling; 4, wrinkling completely distorts fingertip. Wrinkling was assessed by one examiner (AC) blinded to the results of small nerve fibre testing. Foot skin wrinkling was not performed, as wrinkling is poor because of higher sympathetic nerve activity to the lower limbs.[15] As SSW depends on decreased digit pulp volume from vasoconstriction, conditions in which insufficient additional vasoconstriction can be achieved do not favour its application.[9]

IENFD was determined in 3 mm punch biopsy samples from glabrous hypothenar skin.[16]

Analysis

Number and percentage of test abnormality were calculated and compared.

Normal values for nerve conduction were from our local population. SSR was abnormal if absent in two or more limbs. Previously, we established that wrinkling in response to EMLA and water in normal subjects (n = 25, mean age 35 years; range 24–52) was grade 3 and 4, respectively.[7] The lower normal limit for hypothenar IENFD was 1.3 nerve fibres/mm.[16]

RESULTS

Twenty-one patients were included (mean age 55 years (range 22–77); 14 women).

Table 1 shows IENFD, mean EMLA and water wrinkling scores, and SSR data. Sensitivity for diagnosing SFN was 81% (95% CI 58% to 94%) for IENFD, 78% (95% CI 52% to 93%) for EMLA, 80% (95% CI 56% to 94%) for water and 43% (95% CI 21% to 65%) for SSR.

Linear correlation between IENFD and EMLA was reasonable ($R = 0.4468$, $p<0.043$; $t = 2.177$, $df = 19$) but poor between IENFD and water ($R = -0.0997$, $p<0.667$; $t = -0.4367$, $df = 19$). Of 16 (76%) patients with abnormal IENFD, 14 had abnormal EMLA-induced wrinkling and 12 had impaired water-induced wrinkling. EMLA wrinkling was more marked than water wrinkling. SSR was abnormal in nine (43%) patients, of which eight had low IENFD. Water and EMLA showed good correlation ($R = 0.7289$, $p<0.001$; $t = 4.641$, $df = 19$). Of 14 patients with reduced EMLA wrinkling responses, 13 (93%) had reduced IENFD. Two patients showed normal results for all four tests.

DISCUSSION

Few studies have compared multiple variables in SFN. In burning feet syndrome, the sensitivity of IENFD (87.5%) was greater than that of thermal thresholds (72%) and QSART (59%).[3] In a larger group of patients, the same investigators found thermal thresholds to be more sensitive (85%), with good agreement between IENFD (74%) and QSART (68%).[17]

This is the first comparison of a further test of small nerve fibre function, SSW, with IENFD and SSR in diagnosing SFN. Our data show IENFD sensitivity (81%) similar to that of the literature.[1] Although an SFN review recommended SSR because of a lack of commonly available alternatives, our data show SSR to be diagnostically unhelpful.[1] We could not find any other studies that had compared SSR with IENFD in diagnosing SFN. One study of SFN from sarcoidosis showed thermal thresholds to be useful, with SSR abnormal in only seven of 74 patients.[18]

In our study, IENFD was abnormal most often of the four small nerve fibre tests evaluated. Both types of SSW performed well, with sensitivities similar to other established small fibre tests.[1]

Our results showing similar sensitivity for wrinkling and IENFD can probably be explained by the observation that, in SFN, both sympathetic dysfunction—measured by wrinkling—and epidermal nerve abnormality—measured by IENFD—are common and early.[19 20] Taking into account the simplicity of the test, it is remarkable that stimulated wrinkling showed only one (water) and two (EMLA) fewer abnormal results than IENFD. Our results suggest that stimulated wrinkling should be used as a screening test or in settings where IENFD is not available. As there were occasions when the only test showing abnormality was SSW, there is reason to include this test in the standard armamentarium of small fibre tests.

Stimulated wrinkling tests are simple, inexpensive and require no specialised equipment. EMLA has advantages over water, as, from our data, it produces a more linear response curve than water wrinkling and persists for over 90 min, allowing ample time for grading.[9] Training in EMLA-stimulated wrinkling is important to ensure accurate wrinkling scoring. We now have extensive experience with wrinkling and have found good repeatability and inter-observer agreement.[7]

Our study has limitations. We tested only idiopathic SFN with upper extremity symptoms. SFN of other causation, including abnormal glucose metabolism as detected by oral glucose tolerance, should be tested next to ensure applicability

Table 1 Comparison of intraepidermal nerve fibre density (IENFD), stimulated skin wrinkling and sympathetic skin response (SSR) in supporting a diagnosis of small nerve fibre neuropathy

Patient number	IENFD (fibres/mm)	EMLA-induced wrinkling score	Water-induced wrinkling score	SSR
1	0.2	0.0	0.0	Impaired
2	2.6	4.0	3.8	Normal
3	0.1	0.0	1.0	Impaired
4	0.6	0.0	0.0	Impaired
5	5.0	1.7	1.3	Normal
6	0.0	0.3	1.5	Impaired
7	0.0	3.0	3.0	Impaired
8	1.0	0.0	0.3	Impaired
9	1.2	1.0	1.3	Normal
10	0.6	0.0	0.0	Normal
11	0.0	3.0	3.0	Normal
12	3.8	3.3	0.5	Normal
13	1.1	1.0	2.0	Impaired
14	0.9	4.0	4.0	Normal
15	1.7	3.0	3.0	Normal
16	5.2	3.0	0.3	Impaired
17	0.8	1.0	1.0	Normal
18	0.3	0.0	1.3	Normal
19	0.0	1.3	2.3	Normal
20	0.6	0.3	0.3	Normal
21	1.1	0.0	0.0	Impaired

IENFD was abnormal when there were <1.3 fibres/mm, and wrinkling scores were abnormal when <3.

across aetiologies. We tested IENFD in the hand and not the leg because foot wrinkling is unreliable and similar site comparison between tests is necessary.

In conclusion, SSW, which tests postganglionic sympathetic fibres, showed good agreement with IENFD in diagnosing SFN, whereas SSR testing was of little use.

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Notes