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Clinical and electrophysiological evidence of impaired sudomotor function in leprosy patients

Annelies WILDER-SMITH MD DTM&H, *Einar WILDER-SMITH MD DTM&H

*Medical Services International, Hongkong, *Department of Neurology, Singapore General Hospital, Singapore*

Abstract

Anhydrosis contributes significantly to morbidity in leprosy patients. There is evidence that one of the major causes of anhydrosis in leprosy patients is impaired peripheral autonomic dysfunction due to damage of the sudomotor component by Mycobacterium leprae. Histologcial and neurophysiological studies confirm that peripheral autonomic nerve fibres are the initial target of nerve damage in leprosy. Therefore, autonomic function tests might be useful for early detection of neuropathy before there are irreversible motor and/or sensory deficits. To determine frequency and distribution of sudomotor dysfunction in leprosy patients we used the sympathetic skin response (SSR), a simple electrophysiological method based on changes in voltage of the skin in response to autonomic stimuli. In addition, we examined hands and feet for clinical evidence of dryness and also asked for the patient`s subjective impression of dryness. Results were correlated with type and duration of leprosy, as well as with indicators of motor (voluntary muscle testing, VMT) and sensory (touch sensitivity testing, TST) nerve dysfunction. 89 leprosy patients across the clinical spectrum of leprosy were examined. The prevalence of abnormal (defined as absent) SSR in leprosy patients was 60.9%. Clinical examination had a very low sensitivity of 5.3-21.7%, and a specificity of 68.8-88.9%, if SSR was taken as "gold standard". This was also true with patient's subjective impression with sensitivity of 21.1-31.9% and specificity of 70.0-83.3%. There was a trend but statistically no significant difference between prevalence of absent SSR in multibacillary compared to paucibacillary leprosy and also with duration of disease. Absent SSR correlated significantly with severity of motor and/or sensory nerve dysfunction.We conclude that the prevalence of impaired sudomotor function in leprosy is high throughout the clinical spectrum and best detected using SSR compared to clinical parameters. SSR is a simple method and might be of potential use for the detection of early neuropathy.

Key words: leprosy, autonomic nervous system, sympathetic skin response, anhydrosis, autonomic tests

INTRODUCTION

Mycobacterium leprae, the causative organism for leprosy, is the only known bacillus that selectively invades human peripheral nervous tissue.[1] Long-term morbidity and disability in leprosy patients are due to impairment of motor, sensory and autonomic nerve function. Whereas motor and sensory nerve dysfunction have been well documented in leprosy patients, there is considerable lack of research on autonomic nerve dysfunction. Previous reports have identified vasomotor sympathetic abnormalities[2,3,4], autonomic cardiovascular reflex abnormalities[5], and widespread histopathologic involvement of unmyelinated nerve fibers.[6,7]

Autonomic sudomotor functions are also impaired in the disease process causing partial or complete anhydrosis within or outside of leprosy skin patches. Anhydrosis of the limbs contributes considerably to morbidity in leprosy patients as dry skin becomes inflexible and brittle; it fissures easily, thus starting a cycle of ulceration and scarring.[8]

Since Father Joseph Damien first noted the absence of sweating in his own macule of leprosy (1889), absent sweating is looked for as a sign of leprosy. However, before the patient notices any signs and symptoms of neural impairment, extensive damage to nerves has already taken place.[9] Therefore, electrophysiological methods might be of potential use in detecting early sympathetic failure.

The sympathetic skin response is a non-invasive and simple test described recently for studying sudomotor sympathetic function.[10,11] The SSR measures the changes in voltage of the

Address correspondence to: E. Wilder-Smith MD, Department of Neurology, Singapore General Hospital, Outram Road, Singapore 169608

skin in response to exosomatic stimuli.[10] Since there is little data available on peripheral dysautonomia in leprosy, we studied the clinical parameters of absent sweating (hands/feet) along with the skin sympathetic reflex. Furthermore we correlated results with different types of leprosy as well as to the duration of leprosy. In addition the prevalence of autonomic dysfuntion as detected by absent SSR was compared to the commonly used clinical parameters of touch sensitvity testing (TST) and voluntary muscle testing (VMT).

MATERIALS AND METHODS

Patients: Between April and June 1995 patients with confirmed leprosy (according to WHO criteria) between the age of 10 and 55 at the Green Pastures Hospital in Pokhara,West-Nepal, were included into the study. Patients were divided into four groups: 1) newly diagnosed leprosy without treatment; 2) patients with a diagnosis within one year and on standard WHO anti-leprosy treatment; 3) patients with leprosy for more than one year and on treatment; 4) leprosy patients released from treatment.

Excluded were patients with diabetes mellitus, alcoholism, or any other polyneuropathies attributable to other causes than leprosy. As this study was part of a larger study on vasomotor reflex testing in leprosy patients, patients with more than one digit missing or more than one finger pulp with total reabsorption and patients who had undergone surgery at more than one limb were also excluded from the study, as otherwise we would have had too many missing data for digit tip vasomotor reflex testing.

Leprosy patients were classified into multibacillary and paucibacillary according to WHO criteria, as well as into the Ridley-Jopling classification.[12]

The study was approved of by the ethical committee in Berne, Switzerland, and by the local ethics committee in Pokhara, Nepal.

Controls: Healthy controls were recruited from the local Red Cross Society. All controls had no known contact with leprosy.

Clinical examination of hands and feet: both hands and feet were examined by always the same examiner for the subjective impression of dryness and cracks.

Patient's subjective impression: Patients were asked by a Nepali translator if either hands or feet felt dry.

Sympathetic skin response (SSR): Ambient temperature was between 28-33 Celsius. The test was performed in a quiet room. SSR was performed as previously described.[13] Briefly, surface electrodes were attached to the palm and dorsum of either hand as well as to the sole and dorsum of either foot after cleaning with an alcoholic solution. Single square pulses of 200 msec were delivered to the skin of the wrist and ankle. If the skin in that area was anaesthetic, the pulses were applied to a sensitive skin area more proximally. The response was considered absent if no consistent voltage change using a sensitivity of 50 mV/cm was observed after at least 10 trials separated by long intervals to avoid the natural habituation of the response.

Touch sensibility test (TST): A standard set of 5 Semmes-Weinstein monofilaments was used as described by Bell-Krotoski.[14] The score per site varies from 0-5. A score of 5 was given when the thinnest monofilament in the test series was felt (on the hand: 50mg, on the feet 200mg), a score of zero if the thickest filament was not felt. These filaments give a force ranging from 50mg to 300mg for the hand, respectively 200 mg to 300mg for the feet, when applied with enough force to bend the filament. The following sites were tested: *ulnar nerve:* 3 points, on the pulp of the little finger, on the volar skin over the 5th metacarpophalangeal joint and on the hypothenar eminence (max. score 15); *median nerve:* 3 points, on the pulp of the thumb, on the first metacarpophalangeal joint and on the thenar eminence (max. score 15); *posterior tibial nerve:* 4 points: on the tip of the 5th toe, on the plantar skin over 5th metacarpophalangeal joints, the lateral border and the heel (max. 20).

If there was an ulcer on the test site, a score of zero was given for that site.

Voluntary Muscle Test (VMT): VMT was performed using the modified MRC scale as described by Brandsma.[15] The VMT score consisted of the sum of individual scores (0-5; 0, paralysed; 5, normal strength) for muscles innervated by the *ulnar nerve:* first dorsal interosseus and abductor digiti minimi (max. score 10); *median nerve:* abductor pollicis brevis and opponens pollicis (max. score 10); *radial nerve:* extensor carpi ulnaris and extensor digitorum communis (max. score 10); *lateral popliteal nerve:* extensor hallucis longus and peroneus longus & brevis (max. score 10).

Statistical Methods: Data entry and statistical analysis were performed on EPI-INFO Version 6 (Center for Disease Control, Atlanta, Georgia, USA) and SAS Version 6.08 (SAS Inc. Cary, North Carolina, USA).

RESULTS

Patient characteristics: 89 leprosy patients were included with a mean age of 35.0 years (range 11-55). 74% were male. Most patients with leprosy were diagnosed less than one year ago (47%), mean interval to time of diagnosis being 46 months. 32% of the patients had been released from therapy. The distribution of leprosy classification into multibacillary and paucibacillary was equal. According to Ridley-Jopling classification, borderline tuberculoid was the most common type (42%). 47 healthy controls were examined.

SSR: The prevalence of absent SSR was 60.9% in all measured extremities in leprosy patients, with a higher prevalence of absent SSR in the feet (78.6%) versus 43.3% in the hands. The difference between leprosy patients and controls for the prevalence of absent SSR was highly significant ($p<0.001$). (Table 1)

Clinical examination and patient`s subjective impression: 48.5% had loss of sweating as detected clinically and 54% of the patients commented on dryness/subjective loss of sweating in their extremities. Table 2 summarizes above results. There was good correlation between present SSR and present subjective feeling of sweating and clinical detection rate of sweat (70-83.3% and 68.8.-88.9% respectively). In contrast absent SSR correlates poorly with subjective feeling of dryness in the corresponding limb (21.1%-31.9%) and absent SSR also correlates poorly with clinical detection rate (5.3-21.7%). The sensitivity of clinical pick-up rate of dryness by one examiner (if SSR is taken as gold standard)is 5.3-21.7% (and the specificity is 68.8-88.9%. The sensitivity of subjective patient`s impression of dry limbs (with SSR as gold standard) is 21.1-31.9% and the specificity 70.0-83.3%. Results are summarized in Table 3.

TABLE 1: Prevalence of absent sympathetic skin response (SSR) in leprosy patients (n = 89) and healthy controls (n = 47)

	Leprosy patients	Controls	
Hands	43.3%	0	$p < 0.001$
Feet	78.6%	22.2%	$p < 0.001$

SSR in correlation with paucibacillary/ multibacillary leprosy: Patients with multibacillary leprosy had a higher percentage of absent SSR than those with paucibacillary leprosy. However, the difference did not reach the level of significance. (Table 4)

SSR in correlation with duration of leprosy: With increased time elapsed since commencement of treatment prevalence of absent SSR increases , although this trend is statistically only significant for the hands (Table 5).

SSR in correlation to motor (VMT) and sensory (TST) nerve function: There are statistically significant increasing percentages of absent SSR as the severity of motor and sensory nerve dysfunction increases. (Table 6)

DISCUSSION

Our results show that impaired sudomotor function as detected clinically and by absent sympathetic skin response is a frequent finding

TABLE 2: Prevalence (in percentage) of absent sympathetic skin response (SSR), clinical judgment of dry limb, patient's subjective impression of dryness in 89 leprosy patients

	Absent SSR	Dry on clinical examination	Dry according to patient's subjective impression
Right hand	46	49	47
Left hand	43	48	51
Right foot	78	43	60
Left foot	79	54	58

TABLE 3: Sensitivity and specificity (in percentage) of clinical examination and patient's subjective impression of dryness/lack of sweating in the corresponding limb if the sympathetic skin response (SSR) is taken as gold standard

		Clinical examination	Patient's impression
Right hand	sensitivity	14.6	26.8
	specificity	68.8	75.0
Left hand	sensitivity	5.3	21.1
	specificity	72.0	70.0
Right foot	sensitivity	21.7	31.9
	specificity	80.0	70.0
Left foot	sensitivity	21.1	31.0
	specificity	88.9	83.3

in leprosy. This abnormality may result from dermal infiltration by the bacilli with reduction of dermal sweat glands, or be due to reduced or absent neuropeptides associated with sudomotor functions.[16] Furthermore, it may stem from generalized autonomic nervous dysfunction in leprosy.[17] Both immunocytochemical[16] and neurophsyiological studies[2,3,4,18] suggest that peripheral autonomic nerve fiber involvement may be the focus of the initial nerve damage in leprosy. Due to our patient selection criteria, the majority of our patients had leprosy of recent onset and the percentage of patients with advanced deformities was low. For this reason it seems unlikely that direct damage to the sweat glands would contribute significantly to impaired sudomotor function. We propose that absent SSR in leprosy reflects damage to small unmyelinated sympathetic fibers of sudomotor component.

Our study implies that sudomotor peripheral dysautonomia is common in all groups of leprosy patients and has a patchy distribution. The severity of motor and/or sensory deficit correlates significantly with a higher prevalence of sudomotor dysfunction. Our results could only show a trend, but no significant increase in absent SSR findings in correlation with the duration of the disease process. There was a trend but no significant difference between the prevalence of absent SSR in multibacillary compared to paucibacillary leprosy patients.

Detection of anhydrosis with conventional methods such as the anhydrin test are difficult to perform and rarely done. In West-Nepal the only "test" for autonomic dysfunction done is as part of the first routine examination, where the examiner describes a limb as dry or normal. Our study shows that clinical examination for dryness has an unacceptablely low sensitivity if SSR is taken as "gold standard". Although the prevalence of subjective loss of sweating by the patient and by the clinical examiner is high in leprosy patients, both are unreliable methods for early detection of sudomotor function.

As small, poorly or unmyelinated nerve fibers might well be the site of first attack by M. leprae[6,16], neurophysiological methods testing for peripheral autonomic function may be useful in detecting evidence of early defects. Autonomic testing could have potential in the early diagnosis of neuropathy before irreversible damage has occurred. It could also be used for monitoring of anti-inflammatory treatment during leprosy neuritis, although so far data is insufficient to reach conclusions.[19] Of the presently available autonomic tests, vasomotor reflex testing has been previously used in leprosy patients.[2,3,4] However, vasomotor reflex testing is more time consuming and requires adherance to strict protocol.[20]

SSR can be recorded using conventional electromyography and even ECG apparatus and is simple to perform. However, the limitations

TABLE 4: Correlation of absent sympathetic skin response (SSR) with paucibacillary (PB) and multibacillary (MB) leprosy

Limb	PB	MB	Significance
Hands	37.8%	51.2%	x = 3.13 p = 0.074
Feet	73.3%	84.9%	x = 3.53 p = 0.06

TABLE 5: Percentage of absent sympathetic skin response (SSR) correlated to time elapsed since treatment commencement

Limbs	0 – 1 month	2 – 12 months	> 12 months	Released from treatment	Significance test
Hands	46.7	29.6	44.7	57.1	$x^2 = 3.62$ $p = 0.057$
Feet	76.5	75.9	68.4	89.3	$x^2 = 2.08$ $p = 0.149$

of SSR are many. It is a record of an end organ response of a complex multisynaptic reflex and only an indirect evidence of sudomotor nerve function. A number of factors, principally temperature, emotional state and habituation influence it.[21] Although its ease of application supersedes a variety of other autonomic function tests, relying only on SSR changes for prognostication or therapeutic decisions would be imprudent. Our results show a strikingly higher prevalence of absent SSR in the feet compared to the hands, for both the control

TABLE 6: Absent Sympathetic Skin Response (SSR) in correlation with degree of motor (VMT) and sensory (TST) nerve dysfunction in n = 89 leprosy patients

	Degree of severity	n	Absent SSR (%)	Significance
VMT				
Right hand (ulnar & median nerve)	normal	58	17 (29.3)	$x^2 = 20.94$ $p < 0.001$
	moderate	20	13 (65,0)	
	severe	10	10 (100.0)	
Left hand (ulnar & median nerve)	normal	55	12 (21.6)	$x^2 = 24.09$ $p < 0.001$
	moderate	19	14 (73.7)	
	severe	13	11 (84.6)	
Right foot (peroneal nerve)	normal	73	53 (72.6)	$x^2 = 4.86$ $p < 0.027$
	moderate	10	10 (100)	
	severe	6	6 (100)	
Left foot (peroneal nerve)	normal	70	54 (77.1)	$x^2 = 2.01$ $p = 0.156$
	moderate	12	10 (83,3)	
	severe	7	7 (100)	
TST				
Right hand	normal	65	20 (30.8)	$x^2 = 21.75$ $p < 0.001$
	moderate	10	8 (80.0)	
	severe	14	13 (90.9)	
Left hand	normal	60	14 (23.3)	$x^2 = 27.14$ $p < 0.001$
	moderate	17	14 (82.4)	
	severe	11	10 (95.8)	
Right foot	normal	46	30 (65.2)	$x^2 = 8.89$ $p = 0.003$
	moderate	19	16 (84.2)	
	severe	24	23 (95.8)	
Left foot	normal	39	24 (61.5)	$x^2 = 12.56$ $p < 0.001$
	moderate	24	22 (91.7)	
	severe	26	25 (96.2)	

group and for leprosy patients. In the controls there were no absent SSR in the hands, only in the feet. This may be due to the epidermal component of the SSR which is affected by skin thickness.[22] Since Nepali subjects tend to have thicker soles due to frequent barefoot walking, this may well lead to false absent SSR.

We conclude that absent SSR is prevalent throughout the clinical spectrum of leprosy. It is statistically significantly correlated with severity of sensor and/or motor nerve dysfunction but not statistically significantly related to duration of disease. SSR constitutes a more reliable test method for the detection of sudomotor dysfunction than clinical examination and can also be used for early detection of sympathetic failure in leprosy.

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