

Thermoregulatory sweat testing in patients with erythromelalgia.

Thermoregulatory Sweat Testing in Patients With Erythromelalgia

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Objectives: To examine the results of thermoregulatory sweat testing in patients with erythromelalgia and

to compare them with the results of other neurophysiologic tests of small-fiber nerve function.

Design: Retrospective study.

Setting: Tertiary referral center.

Patients: Thirty-two consecutive patients with erythromelalgia who had thermoregulatory sweat testing in addition to vascular and nerve testing.

Intervention: The following information was abstracted for each patient: demographics, clinical presentation, and results of thermoregulatory sweat testing, vascular (noninvasive) testing, and nerve testing (electromyography and autonomic reflex screen, including quantitative sudomotor axon reflex test).

Main Outcome Measures: Results of thermoregulatory sweat testing to evaluate small-fiber neuropathy, compared with other tools used to estimate small-fiber neuropathy.

Results: Thermoregulatory sweat testing results were abnormal in 28 (88%) of 32 patients, and quantitative sudomotor axon reflex test results were abnormal in 22 patients (69%). Abnormalities noted on thermoregulatory sweat testing varied from local hypohidrosis or anhidrosis to global anhidrosis. Global or almost-global anhidrosis was present in 8 patients (25%); in 19 patients (59%) the anhidrosis was distal, and 1 other patient (3%) had a less specific pattern of anhidrosis (multifocal or regional). The area of anhidrosis generally corresponded to the area that was symptomatic of the erythromelalgia.

Conclusions: Small-fiber neuropathy is prevalent in most patients with erythromelalgia. Thermoregulatory sweat testing is a sensitive and useful marker of small-fiber neuropathy in these patients.

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A HIGH PROPORTION OF Patients with the clinical syndrome of erythromelalgia has small-fiber neuropathy, as illustrated by abnormal quantitative sudomotor axon reflex test

(QSART) results and other abnormalities on autonomic reflex screening (ARS).^{1,2} Others report that nerve abnormalities may be associated with erythromelalgia.³⁻⁹ Thermoregulatory sweat testing (TST) is a tool that is increasingly being used to

assess small-fiber neuropathy.¹⁰ Thermoregulatory sweat testing and QSART, another

test of sweating, evaluate the small-diameter nerve fibers that innervate sweat glands in the skin, and test results are usually abnormal in patients with the clinical diagnosis of small-fiber neuropathy. In addition, TST evaluates preganglionic sympathetic fibers and central nervous system autonomic pathways. We observed that results of TST are frequently abnormal in patients with erythromelalgia, which supports the idea that small-fiber nerve abnormalities may underlie erythromelalgia. This has implications for clinical decision making regarding the extent and type of additional evaluations for patients with erythromelalgia.

Therefore, we retrospectively reviewed the results of extensive neurologic and vascular function studies in a group of patients with erythromelalgia in whom TST had been performed as part of the evaluation of small-fiber function. Our objective was to investigate whether TST results are abnormal in patients with erythromelalgia.

METHODS

DEFINITION OF ERYTHROMELALGIA

Erythromelalgia was defined as the clinical syndrome of heat, erythema, and associated discomfort (such as pain, burning tingling, or a similar sensation). These symptoms involve the extremities and occasionally the face.¹¹

PATIENTS

The Mayo Clinic patient database was searched for the records of consecutive patients who had been examined clinically in the departments of dermatology (by M.D.P.D.), neurology, and vascular medicine from January 1, 2003, through December 31, 2004. All patients who fulfilled the clinical definition of erythromelalgia had been evaluated by tests of vascular and neurologic function. The patients' test results were retrospectively examined.

VASCULAR STUDIES

Studies of local vasculature before and during the occurrence of symptoms included laser Doppler flowmetry, measurement of skin temperature, and transcutaneous oximetry. Details of the noninvasive vascular studies used are outlined in previous publications.^{1,2}

NEUROPHYSIOLOGIC TESTING

The neurologic studies performed have been previously described. 1,2 In addition to nerve conduction studies and needle electromyography to assess large-fiber function, ARS (described extensively elsewhere¹²⁻¹⁴) was used to evaluate small fiber function. Autonomic reflex screening included heart rate response to deep breathing and the Valsalva ratio, QSART to quantitatively evaluate the postganglionic sympathetic sudomotor axon reflex (measured on the forearm, proximal lateral leg, distal medial leg, and dorsum of the foot),¹⁵⁻¹⁷ and adrenergic function testing (evaluated from the responses of blood pressure to tilting and the Valsalva maneuvers.¹⁷

THERMOREGULATORY SWEAT TESTING

After adequate preparation, which includes discontinuing any medication known to affect the study and having the patient well hydrated and acclimated to indoor temperature, the anterior body surface of the patient is dusted with an indicator powder.¹⁸ The powder contains alizarin red, which turns from orange to purple when wet. Palmar and plantar skin surface sweating normally is only minimally activated by heating, so the heavily sweating dorsal hands and feet are the preferred distal sites to powder and examine. (Palms and soles are examined only if hyperhidrosis of the hands and feet is part of the

spectrum of patient symptoms.) The patient is then enclosed in a cabinet with a moderately hot and humid environment (45°C-50°C air temperature and 35%-40% relative humidity).

The mean skin temperature is monitored and kept between 38.5°C and 39.5°C by using overhead infrared heaters. The oral temperature, which is close to the core temperature, must rise at least 1.0°C or to 38.0°C (whichever is higher). Maximal sweating is generally achieved in 30 to 65 minutes. At the end of the test, digital photographs of the sweat distribution are taken, and a computerized body image is created that faithfully records sweating (purple indicates wet) and nonsweating (yellow-orange indicates dry) skin as a 2-color pixel density map. This body image map is further processed, counting each colored pixel in addition to summing the pixel densities of a 7_7-pixel cursor (area) that is scanned over the image. The ratio of dry pixel count to the total possible wet pixel count gives the percentage of anhidrosis on the anterior body surface. The software also compares the patient's sweat density map with stored patterns from laboratory control subjects so that normally nonsweating areas (such as bony prominences) or normally hypohidrotic areas (medial thighs and upper medial arms) are accounted for and are not counted as abnormal. Altogether, this processing allows for a useful quantitation of the body surface area that has an abnormal sweat density. The loss of body fluid is also measured during TST as a gross measure of total sweat production, but these data are not reported herein.

INTERPRETATION OF NEUROPHYSIOLOGIC FUNCTION

A consultation with a neurologist specializing in autonomic nerve function was obtained in most patients. A thorough neurologic examination was correlated with TST, QSART, and electromyography results in each patient.

STATISTICAL ANALYSIS

Appropriate summary statistics were used to describe these data. Descriptive statistics were used for the vascular and neurophysiologic studies.

RESULTS

PATIENTS

The records of 32 consecutive patients with erythromelalgia (3 male and 29 female) were identified. All patients were white, with a mean age of 50 years (age range, 17-81 years). Symptoms had been present for 3.6 months to 23 years (**Table**). Erythromelalgia was generally bilateral, involving the feet (29 patients), hands (19 patients), and face (10 patients). A history of Raynaud phenomenon was present in 5 patients. The erythromelalgia was primary in all but 1 patient, who had polycythemia vera.

Twenty-six patients were assessed by a neurologist; the comprehensive neurologic examination in these patients identified normal findings or sensory abnormalities, including hypalgesia or allodynia. Eight of these patients also underwent biopsies during their evaluation. 19 Biopsy results showed no structural abnormalities of the sweat glands.

VASCULAR STUDIES

In all patients undergoing noninvasive vascular testing during symptoms, the expected marked rise in skin temperature and blood flow (measured by laser Doppler flowmetry) was accompanied by a minimal change in transcutaneous oxygen level compared with testing done without symptoms. Symptoms were unable to be elicited in 7 patients during vascular testing; therefore, they only had testing without symptoms.

Patient No.	Symptom Duration at Presentation, y	Erythromelalgia Involvement	Thermoregulatory Sweat Testing Results	Abnormal Quantitative Sudomotor Axon Reflex Test Results
1	0.5	Feet	PA, suggestive of widespread SFN	Yes
2	2	Feet	Anhidrosis (abdomen and legs), suggestive of multifocal SFN	Yes
3	20	Hands, feet	PA affecting LEs, consistent with SFN	Yes
4	0.5	Hands, feet	PA affecting LEs and UEs, consistent with SFN	Yes
5	3	Hands, feet	Scattered areas of H/A of LEs, UEs, and trunk, suggestive of multifocal SFN	Yes
6	7	Feet	H/A of feet, consistent with distal SFN	No
7	0.5	Feet	Almost TBA, suggestive of CIA or diffuse SFN	Yes
8	1	Feet	Normal	No
9	1	Hands, feet	Normal	No
10	2	Hands, feet	PA of LEs and UEs, consistent with distal SFN	Yes
11	2	Hands, feet	PA of LEs and UEs, consistent with distal SFN	Yes
12	2	Hands, feet, face	Normal	No
13	2	Feet	TBA, suggestive of CIA	Yes
14	2	Hands, feet, face	TBA, suggestive of CIA	Yes
15	23	Hands, feet, face	Anhidrosis of toes	No
16	4	Hands, face	Striking anhidrosis of trunk and extremities, suggestive of axonal SFN	Yes
17	4	Hands, feet	AGA with grossly abnormal sweating, suggestive of central ganglionic sympathetic system failure	Yes
18	2	Hands, feet	Anhidrosis (left side affected more than right side) of feet and legs	No
19	2	Hands, feet, face	AGA with small areas of sweating, consistent with diffuse SFN or CIA	Yes
20	5	Hands, feet, face	Painful H/A of LEs and UEs, consistent with SFN	Yes
21	1	Face	AGA with areas of night sweating, suggestive of central autonomic disorder or CIA	Yes
22	7	Feet	Decreased sweating of legs and feet, consistent with distal SFN	Yes
23	1	Hands	Hyperlhidrosis of hands but not feet, consistent with sensory symptoms only in hands	Yes
24	1	Hands, feet	Normal	No
25	2	Feet	Sweating impaired in 4/4 areas of feet and toes, consistent with SFN	Yes
26	3	Feet	Regional anhidrosis, exclusive on LEs and proximal part of UEs	Yes
27	3	Hands, feet, face	Most of body completely anhidrotic, consistent with diffuse SFN	Yes
28	2	Feet	PA of distal part of feet	Yes
29	6	Feet	Anhidrosis of distal part of legs, feet, and toes, consistent with SFN	Yes
30	0.3	Feet	Delayed sweating of distal part of feet and toes, with minor patches of anhidrosis at heel, consistent with SFN	No
31	4	Hands, feet, face	PA of toes, consistent with minimal SFN	No
32	2	Hands, feet, face	Painful decrease in sweating, of undetermined significance	No

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Abbreviations: AGA, almost global anhidrosis; CIA, chronic idiopathic anhidrosis; H/A, hypohidrosis/anhidrosis; LEs, lower extremities; PA, patchy anhidrosis;

SFN, small-fiber neuropathy; TBA, total body anhidrosis; UEs, upper extremities

NEUROPHYSIOLOGIC TESTING

For neurophysiologic testing, QSART was the most relevant component of ARS; results of QSART were abnormal in 22 patients (69%) (Table). The other elements of ARS, including cardiovascular adrenergic function and cardiovagal function (heart rate response to deep breathing test and the Valsalva ratio), showed abnormal results

in 3 patients and in 11 patients, respectively. Electromyography was performed in 27 patients; results were abnormal in 6 patients, demonstrating changes consistent with large-fiber neuropathy.

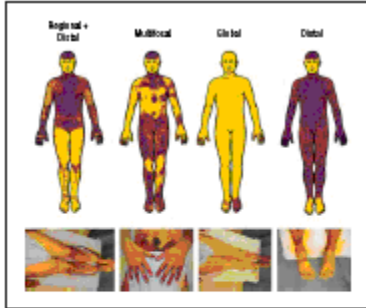


Figure 1. Abnormal thermoregulatory sweat test patterns in patients with erythromelalgia. The most common types of abnormalities in our patients were global (8 patients [25%]) and distal with or without more proximal involvement (19 patients [59%]). Anhidrotic areas are yellow. The clinical photographs below correspond to the thermoregulatory sweat test image directly above them.

THERMOREGULATORY SWEAT TESTING

Results of TST were abnormal in 28 patients (88%) (Table). The most common pattern of abnormality was the distal type, found in 19 patients (59%) and present alone or in combination with more proximal areas of anhidrosis (**Figure 1**). The second most common pattern observed was the global type (anhidrosis on 80% of the body surface), which was present in 8 patients (25%). One patient had a patchy nonspecific distribution of hypohidrosis and anhidrosis. The areas affected by erythromelalgia were generally, but not always, anhidrotic (**Figure 2**).

The results of the tests of sweating were compared. In 6 patients, results of TST were positive when QSART results were negative. There were no cases in which QSART results were positive and results of TST were negative.

Herein, we present 32 consecutive patients with erythromelalgia in whom neurologic evaluations were performed. A diagnosis of small-fiber neuropathy or dysfunction is supported by abnormal TST results in 88% (28/32) of the patients and by abnormal QSART results in 69% (22/32) of the patients; electromyography results support the

presence of large-fiber involvement in only 6 (19%) of 32 patients. These results substantiate previous observations that neuropathy is prevalent in patients with erythromelalgia.^{1,2} The autonomic abnormality observed varies but generally involves only the skin. Typically, results of tests of systemic autonomic function (cardiovascular and adrenergic) are normal, and results of tests of sweating function (QSART and TST) are

abnormal. Orstavik et al^{8,9} noted small-fiber dysfunction in the affected areas of patients with erythromelalgia and suggest that afferent small-fiber dysfunction may help explain the pain associated with erythromelalgia. A pathologic process involving C fibers may be responsible for the pain.⁸ Of the 2 methods for testing the sweating mechanism,

TST is more sensitive than QSART; TST detected sweating abnormalities in 6 more patients than QSART. This result is not surprising given that QSART is only

tested at 4 sites, and the most distal site is on the dorsum of the foot; however, TST assesses the entire anterior body surface and can detect the slightest distal abnormalities

(such as when only the toes are affected).

Furthermore, TST provides a full map of the body, showing specific patterns of abnormality and quantifying the percentage of body surface involved. Thermoregulatory sweat testing is a qualitative and quantitative test of thermoregulatory sweating. Evaluation of the pattern of sweating is qualitative but is based on more than 25 years and 6000 studies of observations of healthy and neurologically abnormal subjects. We established normal variant patterns that are accounted for when determining patterns in patients with erythromelalgia. However, the percentage of anhidrosis is a quantitative

measure derived from digital photographs and computerized body image pixel density measurements.

Because it reflects the sum of many minute areas of the pixel density map, anhidrosis percentage is reproducible in addition to being quantitative. Considering that patients with erythromelalgia have increased pain levels when exposed to heat, it is surprising

that patients can tolerate TST. In fact, the skin temperature is maintained within a narrow range (mean \pm SD, 39.0°C \pm 0.5°C), well above the so-called critical skin temperature

for provocation of erythromelalgia during the test. Some patients with erythromelalgia (perhaps 5%-10%) cannot tolerate the test, but most are accepting of it, perhaps

because TST focuses specifically on their problem. We expected to find altered sweating in the areas affected by erythromelalgia. It was intriguing, then, that 25% (8/32) of the patients had almost global anhidrosis, which suggests more diffuse small-fiber neuropathy or possibly a preexisting condition such as chronic idiopathic anhidrosis.

20 One might speculate whether extensive anhidrosis in some of these patients produces exaggerated alterations in skin blood flow in response to heat and exercise, possibly promoting the development of erythromelalgia.

The finding of 1 patient with a mixed pattern of hypohidrosis and anhidrosis suggests that some patients may have multifocal, albeit only partially symptomatic, small-fiber

dysfunction. Indeed, some patients show normal sweating in areas of erythromelalgia involvement, and some patients show abnormal sweating in areas without erythromelalgia involvement. This lack of correlation is not remarkable; it is occasionally seen in peripheral neuropathies due to well-recognized disorders such as diabetes

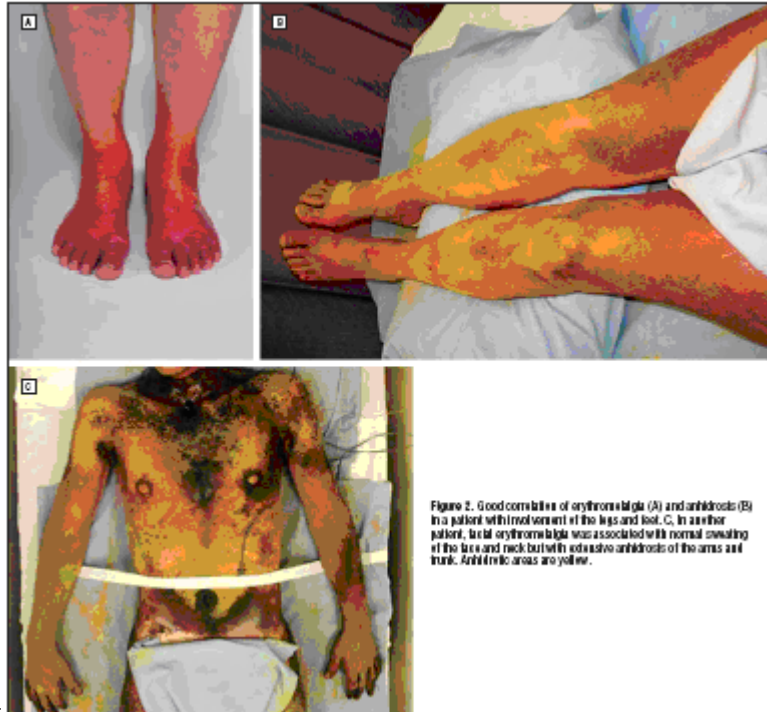
mellitus. Sudomotor axons and nociceptive C fibers differ structurally, so their involvement in a neuropathic process may have different distributions as well.

Furthermore, as already mentioned, the impaired sweating in some patients may reflect a preexisting state that facilitates the development of erythromelalgia. Although we use QSART and TST to evaluate patients with various autonomic disorders and peripheral neuropathies, an abnormal test finding may also result from abnormalities in end organs (eg, the sweat glands). Particularly in the areas where the erythromelalgic manifestations are most dramatic, we cannot rule out the possibility that the sweat reduction is due to trophic skin changes and not to primary small-fiber dysfunction. However, for the 8 patients who had skin biopsy specimens obtained, sweat glands appeared histologically normal.

Erythromelalgia could be a compensatory mechanism for heat loss in patients with hypohidrosis, especially in those with global anhidrosis. Although compensatory

hyperhidrosis might be expected to be the first compensatory mechanism for anhidrosis, in the case of global anhidrosis the body may have to find another way to regulate core temperature, possibly through the mechanism of flushing, as is observed in erythromelalgia. In other words, it is possible that anhidrosis in extensive areas other than the hands might produce reduced sweat heat dissipation, promoting increased vasomotor heat dissipation in body parts having rich vasomotor reactivity such as the hands and feet. Although the palmoplantar regions, which are most frequently severely affected in

erythromelalgia, are not visualized with TST, examination of the heavily sweating dorsal hands and feet is successful in evaluating patients with length-dependent neuropathies in which nerves on the dorsal fingers and toes are as affected as the similar length nerves on the palmar and plantar surfaces. Because ours is a tertiary referral center, we recognize that there is referral bias. The population of patients with erythromelalgia seen at Mayo Clinic is skewed; they are the most severely affected patients, many have disabling symptoms, and many travel a great distance for evaluation.^{11,21} Therefore, the patients in our study may not be representative of the general population of patients with erythromelalgia.



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RESULTS

Results of sweat testing (specifically TST) in patients with erythromelalgia were abnormal in 28 (88%) of 32 consecutive patients. Thermoregulatory sweat testing is a

straightforward, sensitive, and meaningful (to the physician and to the patient) test of small-nerve fiber function that may aid in the diagnosis of underlying small-fiber

neuropathy in patients with erythromelalgia. The results of TST often correlate with abnormal findings in other tests of autonomic or small-fiber function. Abnormal TST results in erythromelalgia are further support for small-fiber neuropathy as a cause of this condition.

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Davis. *Administrative, technical, and material support*: Davis, Genebriera, Sandroni, and Fealey. *Study supervision*: Davis.

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