Primary Erythromelalgia: The Role of Skin Sympathetic Nerve Activity

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A 54-year-old man complained of burning pain, warm skin and erythema in his extremities. A diagnosis of primary erythromelalgia was made. Microneurography was used to clarify the role of skin sympathetic nerve activity in the pathophysiology of primary erythromelalgia. The patient showed normal skin sympathetic nerve activity but no vasoconstriction response. Aspirin activated the skin sympathetic nerve activity and improved vasoconstriction producing symptomatic relief. These results suggest that the lack of vasoconstriction following vasoconstrictor activity of the skin sympathetic nerves results in increased skin blood flow and burning pain.

Key words: Microneurography, Vasoconstrictor fiber, Sudomotor fiber, Aspirin

Erythromelalgia is a rare syndrome characterized by intense burning pain in the extremities that is associated with erythema and the elevation of skin temperature. Various mechanisms have been proposed, but little is actually known about what causes this syndrome. Abnormal microcirculation in the skin provides a clue to the pathophysiology of erythromelalgia.

Skin blood flow is regulated by the vasoconstrictor activity of the skin sympathetic nerves together with local humoral factors. To investigate the role of skin sympathetic nerve activity on the pathophysiology of erythromelalgia, we recorded microneurographically the skin sympathetic nerve activity of a patient with this syndrome using a tungsten microelectrode (1).

CASE PRESENTATION

Case history

A 54-year-old male from Miyazaki Prefecture, Kyushu was admitted because of burning pain in his hands and feet. He had no history of serious illness except for appendicitis at the age of 21. His family history was non-contributory. About 2 yr before admission, he had experienced recurrent episodic attacks of superficial pricking or stinging pain with a burning sensation in the tips of his fingers and toes. Soon after the onset of these attacks the affected area spread over both his hands and feet. This pain worsened in summer, when taking a bath and after local exposure to warmth, even in winter. Generally however, it ameliorated in winter or following exposure to cold. During each episode he noticed that his skin became reddish and that the affected area felt warmer than the other parts of his body. Progression was not apparent.

His height was 161.5 cm, body weight 65 kg, body temperature 36.0°C, pulse rate 60/min and blood pressure 132/60 mmHg. His extremities, especially the palms and soles, were warm. The results of all the other physical and neurological examinations were negative. Subjectively he com-
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plained of pricking or stinging pain in the extremities, but no objective sensory abnormalities were present.

Results of the following tests were within normal limits: erythrocyte sedimentation rate, a complete blood count, blood chemistry assays and urinalysis. An antibody for HTLV-I was positive in his serum, but negative in the cerebrospinal fluid. No atypical lymphocytes were detected in his cerebrospinal fluid. Results of a nerve conduction study were normal, and those of autonomic function tests, the Schel-long, cold pressor, mental arithmetic and nor-adrenaline infusion tests, were within normal limits.

Clinical investigation

Burning pain was produced after the patient’s extremities were immersed in cold water or warmed and by blockage of venous return caused by an inflated pneumatic cuff. A plethysmogram of his second toe showed no vasoconstriction during the immersion of the contralateral part of his foot in cold water. After removal of the cold stimulation, there was a transient increase in the skin blood flow in his foot, but subjectively the intensity of the burning pain was worsened, and simultaneously the detection threshold of vibro-tactile sensation (100 Hz, sine wave) of the big toe was elevated (Fig. 1).

Skin sympathetic nerve activity from the tibial nerve at the popliteal fossa was recorded micro-neurographically with a tungsten microelectrode. The patient gave informed consent to the procedures of this investigation and the study was approved by the Ethical Committee on Human Research of Research Institute of Environmental Medicine, Nagoya University. Basal activity was well preserved, and the reflex burst evoked by electrical stimulation of the ipsilateral median nerve at the wrist showed a biphasic response with normal latency of 0.6 and 1.2 s. Sweat expulsion when the ventilated capsule method was used took place 3.6 s after stimulation, but the plethysmogram

![Threshold of Vibro-Tactile Sensation](image)

**Fig. 1.** Changes in the detection threshold of vibro-tactile sensation and a plethysmogram of the contralateral second toe during immersion of the patient’s foot in cold water (4°C). Upper trace: the patient. Lower trace: an age-matched control subject. The patient showed no vasoconstriction during cold water immersion. When the cold stimulation was removed, the plethysmogram showed an increase in skin blood flow together with a decrease in vibro-tactile sensation.

![Sweat Rate](image)

**Fig. 2.** Changes in the sweat rate, a plethysmogram and integrated skin sympathetic nerve activity after electrical stimulation. A biphasic reflex burst with normal latency is present. Early component: sudomotor activity. Late component: vasoconstrictor activity. The sweat rate increased 3.6 s after electrical stimulation, but there was no vasoconstriction.
Fig. 3. Changes in skin sympathetic nerve activity and a plethysmogram after an aspirin injection. Skin sympathetic nerve activity has been quantified as the burst rate and total skin sympathetic nerve activity. Aspirin activated the skin sympathetic nerve activity and reduced the amplitude of the plethysmogram. Mean ± SD, p<0.01.

showed no vasoconstriction (Fig. 2).

Several minutes after an intravenous injection of 900 mg of aspirin, there was remarkable remission of the burning pain and other symptoms which lasted for several days. Skin sympathetic nerve activity was activated significantly, and the plethysmogram showed an apparent decrease in skin blood flow after aspirin was administered (Fig. 3).

DISCUSSION

Erythromelalgia was first described by Mitchell in 1878 (2). Later Smith and Allen (3) divided this syndrome into primary and secondary forms. This condition occurs in association with numerous disease: polycythemia, hypertension, diabetes mellitus, venous insufficiency and systemic lupus erythematosus (4). In the present patient, these underlying diseases were ruled out and the diagnosis of primary erythromelalgia was made.

The mechanisms of erythromelalgia are not well understood. Theories have been proposed that include a susceptible state of the skin, opening of a subdermal arteriovenous shunt and abnormal metabolism of such vasoactive substances as serotonin and prostaglandins (5).

In the present patient, the transient increase in skin blood flow occurring after immersion of his extremities in cold water was accompanied by an elevation in the detection threshold of vibrotactile sensation which corresponded to worsening of the burning pain. Kikuchi et al (6) reported the same phenomenon and suggested that it is caused by vasodilation and an increase in blood flow in the small blood vessels which is beyond their capacity.

Abnormal microcirculation may be the key to the pathophysiology of erythromelalgia. Skin blood flow is regulated by skin sympathetic nerve activity, local humoral factors, or both. Kitajima et al (7) reported two cases of neuropathy presenting secondary erythromelalgia in which there were high levels of alpha-adrenergic sensitivity and reduced alpha-sympathetic nerve activity. Uno and Parker (8) demonstrated a reduced density of catecholamine-containing nerve terminals in the periarterial plexus and a lack of sympathetic nerve activity in primary erythromelalgia, resulting in the loss of vasoconstriction. Skin sympathetic nerve activity from the tibial nerve is composed of vasoconstrictor and sudomotor components (9, 10). The results of our microneurographic analyses suggested that the somato-autonomic reflex arch was intact and that the vasoconstrictor activity of the skin sympathetic nerve was preserved without the associated response of vasoconstriction. This means that the skin blood flow in our patient is not regulated by vasoconstrictor nerve activity but depends on such local factors as ambient temperature or local vasoactive substances. Blood flow in the skin therefore increases following local exposure to warmth.

Aspirin relieves the symptoms of erythromelalgia, as reported previously by Smith and Allen (3). It is thought that aspirin affects erythromelalgia by inhibiting the action of prostaglandin on platelet aggregation (5); the present patient responded well to aspirin. The mechanism of this action, however, is a matter of controversy because aspirin increases skin sympathetic nerve activity and reduces skin blood flow. Further studies are needed to determine the function of the autonomic nervous system, in particular, the role of skin sympathetic nerve activity in this disease.
REFERENCES