OBSERVATION

Short-term Thallium Intoxication

Dermatological Findings Correlated With Thallium Concentration

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Background: The dermatological features and skin biopsy findings of short-term thallium intoxication have been described. However, the correlation between the dermatological findings and the thallium concentration, the prognosis of peripheral neuropathy, and a cutaneous nerve biopsy study are lacking.

Observations: Two patients initially developed peri-oral numbness, erythematous facial rashes, and polyneuropathy after ingesting thallium-containing water. Severe diffuse alopecia was noted, and a skin biopsy specimen revealed parakeratosis and vacuolar degeneration of the basal layer. Examinations of the hair mount demonstrated a tapered appearance of the anagen root. A serial cutaneous nerve biopsy study showed a loss of epidermal nerves 7 weeks and even 1 year after the thallium intoxication. A toxicology survey disclosed a high concentration of thallium (about 3124 mg/L) in the water. The clinical dermatological features subsided completely, but polyneuropathy with severe painful feet persisted. The blood and daily urinary thallium concentrations decreased slowly in the following 3-month period.

Conclusions: The clinical dermatological features subsided completely, but painful polyneuropathy persisted. The series cutaneous nerve biopsy specimens showed persistent damage to the sensory nerve endings. The disappearance of the dermatological features and the appearance of Mees lines correlated with the decrease of blood and urinary thallium concentrations.

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THALLIUM, A WELL-KNOWN, colorless, tasteless, and odorless heavy metal, is toxic to humans and animals.1 Short-term exposure to thallium may induce hair loss, skin lesions, and damage to the nervous system.2-4 The clinical features of short-term thallium intoxication include the gastrointestinal symptoms of nausea, vomiting, stomatitis, and diarrhea, followed by severe painful dysesthesia and paresthesia in the distal limbs, erythematous rashes in the cheeks and perioral region, and hyperkeratosis and loss of hair in the subacute stage.5-7 In the long-term, complete hair loss and severe polyneuropathy have been noted.8-11

The aims of this study are to find the recovery course of dermatological lesions and skin biopsy findings from these 2 patients with short-term thallium intoxication. In addition, to understand the underlying mechanisms of the burning feet, the cutaneous nerve fiber terminals were studied. We also correlate the series dermatological features and thallium concentrations in the urine and blood.

REPORT OF CASES

Two patients (a 52-year-old husband and a 48-year-old wife) developed the immediate onset of nausea, vomiting, and general aching pain in the muscles and numbness of the tongue and mouth a few hours after drinking about 500 and 750 mL of water, respectively, on March 15, 2002. One day later, severe paresthesia and dysesthesia in both hands and feet...
were experienced. The neurological symptoms gradually worsened, and mixed motor and sensory peripheral neuropathy was noted after nerve conduction studies. The 2 patients underwent forced diuresis and received laxative treatment initially and activated charcoal and Prussian blue, 1 g/d, in 4 divided dosages after thallium intoxication was confirmed 3 weeks later. The Prussian blue treatment was continued for 3 months until the thallium concentration returned to normal ranges. In addition, prolonged hemoperfusion (10 hours) was performed twice 2 months after thallium intoxication was confirmed 3 weeks later. The Prussian blue treatment was continued for 3 months until the thallium concentration returned to normal ranges. In addition, prolonged hemoperfusion (10 hours) was performed twice 2 months after thallium intoxication in patient 1 and 48 days after thallium intoxication in patient 2 because of a high urine thallium concentration.

### METHODS

#### CLINICAL FOLLOW-UP

The clinical manifestations, particularly the dermatological features, were charted closely during the 1-year follow-up. In addition, skin lesions, including rashes, hair loss, follicular plugging, and Mees lines were emphasized.

#### SKIN BIOPSY SPECIMENS

Skin biopsy specimens were taken from the face of the 2 patients, after informed consent, 2 weeks after admission. The skin specimens were fixed and stained with hematoxylin-eosin and, particularly, rhodizonate, which could stain the thallium. Scalp hairs were removed from these 2 patients and examined under a light microscope and a polar light microscope. A skin biopsy specimen was also taken from the right hand and foot, 7 weeks and 1 year later, because of persistent sensory symptoms. The ethics committee approved the protocol. Skin samples were fixed with 4% paraformaldehyde in 0.1M phosphate buffer, pH 7.4, for 48 hours. Then, 50-µm sections were cut on a sliding microtome (Model 440E; Microm, Walldorf, Germany). Sections were treated with nonionic surfactant (0.5% Triton X-100; Structure Probe, Inc/SPI Supplies, West Chester, Pa) in 0.5M Tris buffer, pH 7.6, for 30 minutes, and processed for immunostaining. After quenching with 1% hydrogen peroxide and blocking with 5% normal goat serum, sections were incubated with rabbit antiserum to protein gene product 9.5 (dilution, 1:1000) [UltraClone, Isle of Wight, England] for 16 to 24 hours. Biotinylated goat antibody (Vector, Burlingame, Calif) and avidin-biotin complex (Vector) were respectively applied later for 1 hour. The reaction product was demonstrated by chromogen SG (Vector)."
RESULTS

CLINICAL FOLLOW-UP

The demographic data and clinical findings are summarized chronologically in Table 1. Erythematous lesions appeared in the cheeks and perioral region in the first week and developed into acneiform or pustular eruptions (Figure 1). Hair loss started in the third week and was complete within 2 months (Figure 2). Hair regrowth started 2 months later and was completed after 2 months. Scaling with hyperkeratosis was noted in the index finger of patient 1 and in the bilateral soles of patient 2 in the fourth week. Mees lines were noted in the fingernails and toenails of patients 1 and 2, in the second and third months, respectively (Figure 3).

For sensory function, paresthesia or dysesthesia developed on the second day, and hypoesthesia was observed 2 weeks later. Persistent paresthesia and dysesthesia were noted for more than 1 year. For motor function, tendon reflexes were hyporeflexic 2 weeks later. Muscle strength showed a rapid deterioration 2 weeks later and reached a maximal deficit within a month. In the following year, a slow recovery of muscle strength was noted.

SKIN BIOPSY SPECIMENS

A skin biopsy specimen taken from the crusted eczematous lesions of the face of patient 1 showed marked parakeratosis, dilated hair follicles filled with keratin and necrotic sebaceous materials, and mild epidermal atrophy and vacuolar degeneration of the basal layer (Figure 4). Perivascular and periadnexal infiltrates of mononuclear cells were also found. The skin specimens stained with rhodizonate revealed no thallium deposition.

A skin biopsy specimen taken from the facial lesions of patient 2 showed characteristics similar to those of her husband. The hair roots sampled during short-term hair loss and after recovery of alopecia were compared under a light microscope (Figure 5). Under a polarized light microscope, tapering and darkening of the hair roots were noted.

CUTANEOUS NERVE STUDY

During the first cutaneous nerve study 7 weeks after thallium intoxication, skin innervation was markedly reduced in these 2 patients. Epidermal nerve fibers were almost completely absent in most sections. Degenerating dermal nerves exhibiting a fragmented pattern were prominent in the subepidermal regions. During the follow-up cutaneous nerve study 1 year later, the epidermal nerve fibers were still absent and degeneration of the dermal nerves were still present compared with a healthy control subject (Figure 6).

TOXICOLOGY SURVEY

A high concentration of thallium (3124 mg/L) was noted in the pot water, which proved eventually to be homi-
cidal from the unidentified family member. The heavy metal survey of the 24-hour urine specimens with inductively coupled plasma mass spectrometry showed high concentrations of thallium, with 22,650 µg/d in patient 1 and 29,040 µg/d in patient 2 (reference range, 0-3 µg/d), while the levels of mercury, lead, cadmium, arsenic, manganese, nickel, zinc, copper, bismuth, tellurium, and antimony were unremarkable. The blood thallium levels were 950 ng/g in patient 1 and 2056 ng/g in patient 2 on the fourth day after short-term intoxication. The serial 24-hour urinary and blood thallium concentrations are shown in Table 2.

**COMMENT**

The present study reports the chronological changes in the dermatological features of 2 patients with short-term thallium intoxication from pot water, which eventually proved to be deliberately tainted. Patient 2 ingested a relatively larger amount of thallium than patient 1 (the estimated dosage of thallium was about 2.3 g in patient 2 and 1.5 g in patient 1). The clinical dermatological features of patient 2 were more prominent than those of patient 1.

Short-term thallium intoxication may induce numbness in the perioral region and loss of taste, followed by severe dysesthesia, paresthesia, and even allodynia.1-4 The symptoms may progress rapidly to severe polyneuropathy and cranial neuropathy, and even to respiratory failure. Previous nerve biopsy studies1,4 have revealed primary axonal degeneration with secondary myelin degeneration. In the electron microscopic examination, large and medium nerve fibers were damaged selectively. In our patient, the small sensory fibers were also damaged, with persistent, severe, painful sensory im-
pairment 1 year later, even after the clinical dermatological pictures completely subsided. In addition, the serial cutaneous nerve biopsy specimen with protein gene product 9.5 staining also confirmed damage to the small sensory fiber terminals 1 year later.

The initial mucocutaneous signs, including acnelike lesions on the face, scaling of the palms and soles, stomatitis, and painful glossitis, have not been specific. During the second to third weeks, the loss of scalp hair and the lateral aspects of the eyebrows develop, with a relative preservation of the eyelashes, pubic hair, and axillary hairs. Dark pigmentation of the hair roots and black, tapered, dystrophic anagen roots can be found. However, the dark regions are an optical phenomenon caused by the accumulation of gaseous inclusions that diffract the light. In the skin biopsy specimens of our patients, marked parakeratosis, dilated hair follicles with keratin and necrotic sebaceous materials, and vacuolar degeneration of the basal layer were found. The findings were similar to those of previous studies of short-term thallium intoxication. However, in the rhodizonate staining test, which could stain thallium as dark black, there was no detectable thallium deposition. Animal studies have suggested that thallium affects hair follicles directly or through its effects on the sympathetic nervous system. Our data indicated that cutaneous manifestations might be induced by a more complex pathogenesis, instead of a direct toxic effect of thallium.

In previous studies, thallium has had an affinity for sulfhydryl groups and has interfered with sulfhydryl-containing enzymes, which are highly rich in the skin tissue. Cysteine is a sulfhydryl-containing amino acid, and many cysteine residues can cause insolubility and resistance to the stretching of keratin bonds and account for the alopecia in short-term thallium poisoning. The series cutaneous nerve biopsy specimens revealed denervation of the epidermis and total loss of the epidermal nerves and fragmented nerves in the subepidermal region 7 weeks and 1 year later, compatible with sensory neuropathy with dysesthesia and paresthesia in short-term thallium intoxication. The data indicated persistent damage to the small sensory nerve fiber terminals even after 1 year.

From the interval of the appearance of Mees lines, patient 2 had a delayed appearance of Mees lines than that in patient 1, indicating that thallium might inhibit the protein synthesis of the nail and then interfere with nail growth.

Table 2. Blood Concentrations and Daily Urinary Excretion of Thallium in 2 Patients With Short-term Thallium Intoxication*

<table>
<thead>
<tr>
<th>Time, d</th>
<th>Patient 1</th>
<th></th>
<th>Patient 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urine Excretion, µg/d</td>
<td>Blood Concentration, ng/g</td>
<td>Urine Excretion, µg/d</td>
<td>Blood Concentration, ng/g</td>
</tr>
<tr>
<td>4</td>
<td>22,650.2 (100.0)</td>
<td>950.0 (100.0)</td>
<td>29,040.0 (100.0)</td>
<td>2,056.0 (100.0)</td>
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<td>30</td>
<td>NA</td>
<td>300.0 (32.2)</td>
<td>NA</td>
<td>455.0 (22.1)</td>
</tr>
<tr>
<td>47</td>
<td>97.7 (4.3)</td>
<td>132.0 (13.9)</td>
<td>1177.9 (4.1)</td>
<td>23.6 (1.1)</td>
</tr>
<tr>
<td>48</td>
<td>NA</td>
<td>132.0 (13.9)</td>
<td>435.6 (1.5)</td>
<td>23.6 (1.1)</td>
</tr>
<tr>
<td>52</td>
<td>107.0 (11.3)</td>
<td>81.0 (8.5)</td>
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<td>15.4 (0.7)</td>
</tr>
<tr>
<td>59</td>
<td>692.2 (3.1)</td>
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<td>12.4 (0.6)</td>
</tr>
<tr>
<td>61</td>
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<td>7.5 (0.4)</td>
</tr>
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<td>38.7 (0.2)</td>
<td>1.9 (0.2)</td>
<td>NA</td>
<td>4.7 (0.2)</td>
</tr>
</tbody>
</table>

Abbreviation: NA, data not available.

*Data are given as number (percentage). Percentages are based on the values given on day 4.

Figure 6. Cutaneous nerve study specimens immunostained with protein gene product 9.5 revealed a nearly complete loss of epidermal nerves 7 weeks after short-term thallium intoxication (A) and 1 year later (B), compared with a healthy control (C). The bar denotes 50 µm.
that thallium concentration that causes hair loss and inhibits hair regrowth. Hair loss was observed in rats exposed to 1.2 mg/kg of thallium per day or more for 15 weeks. In one study, in which a patient was administered radioactivity, half of the radioactivity was detected in the urine 21.7 days after exposure. In our patients, the thallium concentrations in the blood were decreased to 306.0 ng/g (32.2%) in patient 1 and 455.0 ng/g (22.1%) in patient 2 one month later, possibly because of treatment with laxatives and Prussian blue and forced diuresis. During prolonged hemoperfusion for 10 hours, the urinary thallium levels seemed to decrease rapidly. In our study, the excretion of thallium from urine was slow and took more than 3 months. In addition, the improvement of dermatological features also took about 2 to 3 months. Although the potential toxic level for dermatological changes was not known, the recovery of dermatological features was thoroughly correlated with the decrease in urinary and blood thallium concentrations in these 2 patients.

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Author Contributions: Drs Lu and Huang contributed equally to this work. Study concept and design: Huang. Acquisition of data: Huang, Tsai, Kuo, Chuang, and Shih. Analysis and interpretation of data: Lu, Huang, and Chang. Drafting of the manuscript: Lu, Huang, Tsai, and Kuo. Critical revision of the manuscript for important intellectual content: Huang and Chang. Statistical analysis: Huang. Obtained funding: Huang. Administrative, technical, and material support: Lu, Huang, Chang, Kuo, and Shih. Study supervision: Huang.

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REFERENCES