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Observational Study

Early diagnosis, treatment, and outcomes of five patients with acute thallium poisoning

Early diagnosis of acute thallium poisoning

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Abstract

BACKGROUND

Thallium poisoning is rare and difficult to recognize. Early diagnosis and treatment of thallium-poisoned patients are essential to prevent morbidity and mortality.

AIM

To evaluate the efficacy of treatments and outcomes of five patients with early diagnosis of acute thallium poisoning.

METHODS

Five patients who consumed a thallium-contaminated meal were hospitalized in succession, and underwent clinical examinations such as blood tests and electromyography tests. Urine and blood tests confirmed the diagnosis of thallotoxicosis, revealing the occurrence of food poisoning. All patients underwent detoxification treatment, including hemoperfusion and treatment with Prussian blue. A 24-month follow-up was performed to evaluate the long-term outcomes on the patients after discharge.

RESULTS

Initially, the patients presented with symptoms of acute thallium poisoning included hyperalgesia of the limbs and abdominalgia, which may differ from common peripheral neuropathy. Accompanying symptoms such as hepatic damage and alopecia were observed in all the patients, which further confirmed the diagnosis of poisoning. Treatment with chelating agents were ineffective, while hemoperfusion and treatment with Prussian blue drastically decreased the thallium concentration in the urine and blood. With early diagnosis and intervention, four patients had a good prognosis and no permanent sequelae. One patient developed blindness and disability during the 24-month follow-up period.

CONCLUSION

Identification of incident cluster and characteristic symptoms are extremely important for early diagnosis of acute thallium poisoning. Hemoperfusion plus Prussian blue are essential to improve the prognosis of thallium-poisoned patients.

Key Words: Thallium poisoning; Hyperalgesia; Abdominalgia; Hemoperfusion; Prussian blue; Outcomes

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Core Tip: Thallium poisoning is rare and easily to be misdiagnosed. In this study, dysesthesia of limbs with hyperalgesia and abdominalgia were the main initial symptoms of the five patients who had a thallium-contaminating meal together. The diagnosis was confirmed by high thallium concentrations in the blood and urine samples which were detected 8 to 12 days after exposure. We found that early treatment with the combination of hemoperfusion and Prussian blue significantly decreased the concentration of thallium in the body and improved the prognosis. Our study provided valuable experiences on early diagnosis and therapeutic regimen for thallium-poisoned patients.

INTRODUCTION

Solutions of thallium salts are colorless, tasteless, odorless, and highly toxic, with an estimated lethal dose ranging between 10–15 mg/kg [1-3]. Symptoms of the nervous system, such as polyneuropathy, comatose, seizures, memory impairment, and mental disturbance may be the first and characterized outcome of acute thallium poisoning [4-6]. Recently, cases of acute thallium poisoning have been reported in developing countries, including China [7-9]. However, since the clinical features in the early stages of acute

thallium poisoning are difficult to identify, most patients are misdiagnosed and develop sequelae of poisoning [10, 11]. Fatality has been reported in patients whose hospital admissions were delayed [11-14]. Mortality due to thallium poisoning was reported to be between 6–15% [15]. Therefore, early diagnosis and appropriate treatment are crucial for patients with acute thallium poisoning.

In this study, we report the symptoms, treatment, and outcomes of five patients with acute thallium poisoning after consuming a thallium-contaminated meal. The first two patients were successively hospitalized with similar clinical symptoms, which prompted us to identify the history of exposure to the toxicant and immediately initiate a detoxification treatment. We made a rapid diagnosis of acute thallium poisoning. Similarly, the history of exposure to toxicant in the other three patients were noted, and they received targeted therapies, including hemoperfusion (HP) and Prussian blue (PB). At the 24-month follow-up, four patients (80%) did not develop permanent sequelae, and no deaths were observed. Our study provides valuable insights into the early diagnosis and treatment of patients with acute thallium poisoning.

MATERIALS AND METHODS

On September 11, 2016, a 40-year-old man was hospitalized with pain and weakness of the distal limbs for one day. Subsequently, a day later, the second patient, who developed pain in the lower limbs and lower back was admitted. Both patients were initially diagnosed with peripheral neuropathy, and conventional treatments including vitamin B and pregabalin were ineffective. In a symposium, the attending physicians noticed that the two patients had similar complaints and syndromes, and traced their histories carefully. They identified that they had attended a banquet, where they had dinner one day before the first patient was admitted. The other three patients who attended the banquet were traced and hospitalized.

All five patients underwent routine examinations, including blood tests and electromyography (EMG). The clinical manifestations and results of the clinical examinations were recorded in detail. Following the realization that this was a mass

poisoning, we rapidly evaluated for toxicants in the urine and blood samples, and found elevated thallium concentrations in all five patients. Initially, the patients underwent detoxification treatment with chelating agents [intravenous injection of 0.64 g of sodium thiosulfate per day and intramuscular injection of 0.25 g of dimercaptopropane sulfonate (DMPS) twice daily], HP, and oral administration of PB (3.3 g in 50 mL of mannitol, four times daily). During the 24-month follow-up study after discharge, the symptoms were recorded for months 1, 3, 12, and 24, while EMG, Mini-Mental State Examination (MMSE), Hamilton Anxiety Rating Scale (HAMA), Hamilton Depression Rating Scale (HAMD), and Modified Rankin Scale (mRS) assessments were performed in month 12.

RESULTS

Clinical characteristics

All five patients were male, aged 33 to 49 years old, and were related to each other. The first (patient 1), fourth (patient 4), and fifth (patient 5) patient were from the same family, and the second (patient 2) and third patient (patient 3) were their co-workers. The day before patient 1 was hospitalized, all the patients had consumed a thallium-contaminated meal together. Patient 1 developed numbness and pain in the distal extremities, approximately 24 h after having the thallium-contaminated meal. On admission, physical examination revealed bilateral hyperalgesia below the wrist and knees. The patient experienced severe pain of the skin of the aforementioned regions upon palpation by the examiner, or by using cotton swabs. Additionally, patient 1 suffered from bilateral weakness of the lower limbs. About 48 h after the consumption of the thallium-contaminated meal, patient 2 was admitted to another ward of the same hospital with complaints of numbness of the lower limbs and a pain that rapidly radiated from the bilateral feet to the waist. Additionally, he rapidly developed numbness in the fingers after hospitalization. Since the symptoms of the two patients were similar, we traced their history of consumption, after which we found that they knew each other and had consumed a meal together. Considering that it may be an

incident cluster of suspected food poisoning, we contacted and hospitalized three other patients who attended the same event and observed that they had already developed symptoms of abdominalgia and numbness or weakness of the distal limbs, which appeared within 48–120 h after having the meal. During hospitalization, the gastrointestinal symptoms including abdominalgia, loss of appetite, nausea, and vomiting progressively aggravated, and the hepatic damage was persistent in all five patients (100%). Subsequently, all patients (100%) developed skin lesions primarily characterized by dry and cracked skin on the lips, back of the fingers and toes, and alopecia. Transient coagulation dysfunction was observed in two patients (40%, patients 1 and 3) on day 11 after exposure, without any symptoms of bleeding. Three patients (60%, patients 1, 3, and 5) developed symptoms of the central nervous system, including somnolence and decreased responsiveness on days 12–15 after onset. Patient 1 presented with psychiatric symptoms characterized by emotional lability and verbal aggression. The primary clinical features of the patients are summarized in Table 1.

Laboratory findings and results of EMG

After admission, the blood tests of all five patients (100%) revealed hepatic damage, mainly characterized by elevated alanine aminotransferase (ALT) levels. Creatine kinase-MB (CK-MB) levels were increased in three patients (60%; patients 1, 3, and 4). Two patients (40%, patients 1 and 3) developed coagulation dysfunction on day 11 after exposure; however, the level of prolonged activated partial thromboplastin time (APTT) returned to normal immediately in the following days. EMG was performed for all the patients (100%). Nerve conduction studies revealed normal results in two patients (40%, patients 2 and 4), whereas the other three patients (60%, patients 1, 3, and 5) showed attenuated amplitude of sensory nerve response of the sural and median nerves, which were considered as mild injury (decreased amplitude < 20%). Only patient 1 (20%) developed moderate injury of the motor nerve in the lateral median nerve (decreased amplitude 26%) (Table 2).

Diagnosis and treatment

The urine and blood samples of the first two patients were immediately sent to Hospital 307 of Chinese People's Liberation Army after the diagnosis of food poisoning. The heavy metal content was determined using atomic absorption spectrophotometry. It was revealed that the thallium concentration exceeded the threshold limit value (> 1000 times) in urine (ref: < 5 μg/L; patient 1, 7200 μg/L; patient 2, 5100 μg/L) and blood (> 100 times) (ref: < 2 μg/L; patient 1: 280 μg/L; patient 2: 210 μg/L). Samples from the other three patients were examined immediately after hospitalization.

The diagnosis of all the patients was confirmed within 12 days of exposure. The patients underwent rapid detoxification treatment with sodium thiosulfate (3–11 days after exposure). After diagnosis, patient 2 was transferred to Hospital 307 of Chinese People's Liberation Army to undergo HP and treatment with PB on day 10 after the exposure, while patient 1 temporarily stayed in the original hospital and received DMPS treatment owing to economic constraints; however, the symptoms were not significantly alleviated. Approximately 15 days after the exposure, all patients, except patient 2, were transferred to Hospital 307 of Chinese People's Liberation Army to undergo HP and treatment with PB, which lasted for approximately two weeks. After treatment, there was no detectable thallium in the blood of all the patients. Moreover, the thallium concentration in the urine decreased significantly, and only a low concentration was detected in patient 1 (160 μg/L) and patient 2 (120 μg/L). The details of the treatment and concentrations of thallium before and after treatment are presented in Table 3.

Outcomes

After discharge, follow-up visits were performed at 1, 3, 12, and 24 mo post-detoxification treatment. During the first follow-up in month 1, symptoms of alopecia and dysesthesia of the fingers or limbs persisted in all the patients. Additionally, patient 1 suffered from symptoms of the central nervous system characterized by bradypsychia and cranial nerve dysfunction such as blepharoptosis, and patient 5 developed mild dysphasia. In the third month after discharge, all five patients (100%) had severe alopecia. Symptoms of peripheral neuropathy, such as hypalgesia or weakness of the

limbs persisted in three patients (60%, patients 1, 2, and 5). Patient 1 developed symptoms of cognitive impairment and nystagmus, which indicated a deteriorated neurological outcome. Patients 2 and 5 (40%) complained of bradypsychia. During the 12-month follow-up, the original symptoms of four (80%) patients markedly improved, except for patient 1, who developed blindness and dysphagia. At the 24-month follow-up, patient 1 was paralyzed and unable to take care of himself, while the other four patients returned to normal life without any symptoms (Table 4).

At 12-months after discharge, EMG, MMSE, HAMA, HAMD, and mRS assessments were performed on all five patients. EMG revealed reduced amplitudes and conduction velocities of sensory nerves in four patients (80%, patients 1, 2, 3, and 5). Based on nerve conduction studies, patients 1 and 5 (40%) were diagnosed with motor neuropathy. In particular, the severely reduced motor conduction velocity of the bilateral tibial nerve and moderately decreased amplitude of the sensory nerve action potential of the bilateral tibial nerve, sural nerve, and median nerve indicated significant and persistent demyelination and axonal damage of the motor and sensory nerves in patient 1. MMSE revealed a very low score (5 points) in patient 1 (20%), while the other four patients had a score within the normal range, according to their educational level. Due to severe cognitive impairment, patient 1 was unable to complete the HAMA and HAMD assessments. HAMA and HAMD assessments in the other four patients demonstrated that patient 3 had both depression and anxiety, while patient 4 had anxiety alone. The mRS assessment was performed according to the scoring system described by van Swieten *et al* [16]. The mRS score of patient 1 was evaluated to be 4, due to severe disability. The other four patients (80%) had a good prognosis and had an mRS score of 0. The outcomes of the assessment at the 12-month follow-up are listed in Table 5.

DISCUSSION

Thallium is a rare but an extremely toxic metal. Events of thallium poisoning are punishable by law and can be filed as homicide by poisoning. Peripheral neuropathy and gastrointestinal symptoms are the two primary symptoms of the onset of acute

thallium poisoning [17]. Usually, patients tend to neglect abdominalgia, which prompts them to consult a neurologist and get misdiagnosed with Guillain-Barre syndrome. In this study, patients 1 and 2, who had high thallium concentrations, developed symptoms of hyperalgesia earlier prior to the gastrointestinal symptoms, indicating that the concentration of thallium may be related to peripheral neurotoxicity. Accurate recognition of symptoms of metal poisoning is valuable for the differential diagnosis. For patients with lead poisoning, the symptoms of abdominal pain and headache are more severe, and motor nerve involvements are more common. Peripheral neuropathy is also frequently observed among patients with arsenic poisoning, but skin lesions and pigmentation could be the characteristic appearance. Concentration of thallium in the blood and urine should be < 2 μg/L and < 5 μg/L respectively in healthy individuals, and the diagnosis of thallotoxicosis relies on abnormally elevated levels of thallium in the blood or urine [2, 18]. The inability to detect heavy metals in the blood or urine in primary hospitals could be another cause of delayed diagnosis. However, for the differential diagnosis between peripheral neuropathy and poisoning, distinctive clinical signs such as hyperpathia, abdominalgia, and alopecia, which are common in thallium poisoning, and the elevation of creatine kinase and liver enzymes should be monitored at onset [19, 20]. We retrospectively reviewed studies on acute thallium-poisoned patients with identified intervals from onset to diagnosis and outcomes. In our case series, the mean interval from exposure to diagnosis was 10.4 days, which is much shorter than the typical interval of 23.6 days in previous publications (The references are labeled in Table 6). Although the concentration of thallium and the treatment methods varied, early diagnosis was accepted as the key for patients to achieve good prognoses (Table 6).

There exists a lack of controlled trials to recommend a specific antidote against thallium poisoning. Based on the diagnostic criteria of occupational thallium poisoning of P.R. China (GBZ226-2010), the use of traditional chelators such as dimercaptosuccinic acid (DMSA) against thallium poisoning could be a reference for clinical prescriptions. However, recent evidence has discouraged the use of chelators because of the lack of

apparent benefits in controlled trials in animals [28, 29]. It was reported that the application of sodium diethyldithiocarbamate may cause redistribution of thallium into the central nervous system [30]. In our study, the first two patients received early treatment with sodium thiosulfate for detoxification, before the diagnosis of thallotoxicosis was confirmed. The treatment seemed to be ineffective as the thallium concentrations in the plasma and urine were still very high in the patients, when they were tested a few days later. Three patients with different concentrations of the toxicant developed symptoms of the central nervous symptoms during sodium thiosulfate treatment, and transient coagulation dysfunction was observed in two of them without any symptoms of bleeding or decline in platelet count. It remains elusive whether transient coagulation dysfunction is associated with sodium thiosulfate treatment. Existing data supports treatment with PB as an effective therapy against acute thallium poisoning, although this drug is not widely available and the side effects need to be considered [31]. In recent studies, the combined use of PB and HP or plasma exchange enhanced the elimination of thallium in animals and humans, and improved survival of the patients, especially those whose hospital admission were delayed [9, 10, 32, 33]. All our patients received PB plus HP, and the levels of the toxicant drastically and rapidly decreased after the treatment.

In our patients, most of the symptoms at the onset of thallotoxicosis gradually disappeared during the first year of follow-up. EMG revealed that the injury of the sensory nerve was more severe than that of the motor nerve and persisted 12 mo post-discharge. Data presented in previous studies revealed that the concentration of thallium intoxication is associated with prognosis [12, 13]. In this case series, patient 1, whose thallium concentration was the highest, developed severe disability, while the other four patients recovered well. Notably, patient 2, who also had a high thallium concentration, did not develop permanent sequelae, as he received treatment with PB and HP five days earlier than patient 1. There are several limitations to this study. Since it was a criminal event, we were unable to recall the patients to the hospital to conduct detailed examinations during the early phase of the follow-up until the suspect was

identified. Since the sample size was small and no control group was established, most of our findings were observational and descriptive.

CONCLUSION

The early diagnosis of acute thallium poisoning in the five patients was made with the following indications: clustered cases, specific presenting symptoms such as hyperalgesia and abdominalgia, and abnormal laboratory findings with elevated ALT and CK-MB levels. Treatment using PB and HP could be effective therapy against thallotoxicosis, since it rapidly eliminates the thallium concentration.

ARTICLE HIGHLIGHTS

Research background

Acute thallium poisoning is rare and hard to identify. Patients with thallium poisoning are usually misdiagnosed at the early stage and develop permanent sequelae.

Research motivation

We hope that this study can provide a reference for the early diagnosis and treatment of patients with acute thallium poisoning.

Research objectives

To analyze the clinical characteristics of five patients with early diagnosis of acute thallium poisoning, and to evaluate the efficacy of treatments and outcomes.

Research methods

The symptoms, treatment, and outcomes of five patients with acute thallium poisoning after consuming a thallium-contaminated meal were recorded and analyzed.

Research results

Patients with acute thallium poisoning developed hyperalgesia of the limbs and abdominalgia, which may differ from common peripheral neuropathy. With early diagnosis and intervention, only one patient developed serious sequelae during the 24-month follow-up.

Research conclusions

Identification of incident cluster and characteristic symptoms are crucial for the early diagnosis of acute thallium poisoning. Hemoperfusion and Prussian blue could be an effective therapeutic option to improve the prognosis of acute thallium-poisoned patients.

Research perspectives

More patients should be observed with control group to make the conclusions more reliable.

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