**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 63923

**Manuscript Type:** ORIGINAL ARTICLE

***Observational Study***

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

Wang TT *et al*. Early diagnosis of acute thallium poisoning

Ting-Ting Wang, Bing Wen, Xiu-Nan Yu, Zhang-Ge Ji, Yi-Yong Sun, Ying Li, Shou-Lian Zhu, Yong-Liang Cao, Mei Wang, Xiang-Dong Jian, Tan Wang

**Ting-Ting Wang, Xiu-Nan Yu, Zhang-Ge Ji, Yi-Yong Sun, Ying Li, Shou-Lian Zhu, Yong-Liang Cao, Mei Wang,** Department of Neurology, Zibo Municipal Hospital, Zibo 255400, Shandong Province, China

**Bing Wen,** Department of Neurology, Qilu Hospital of Shandong University, Jinan 250012, Shandong Province, China

**Xiang-Dong Jian,** Department of Poisoning and Occupational Diseases, Qilu Hospital of Shandong University, Jinan 250012, Shandong Province, China

**Tan Wang,** Department of Geriatrics, Qilu Hospital of Shandong University, Jinan 250012, Shandong Province, China

**Tan Wang,** Key Laboratory of Cardiovascular Proteomics of Shandong Province, Qilu Hospital of Shandong University, Jinan 250012, Shandong Province, China

**Author contributions:** Wang TT and Wen B analyzed and interpreted the patient data and designed the follow-up work; Yu XN, Ji ZG, Sun YY, Li Y, Zhu SL, Cao YL, and Wang M provided the patient data; Jian XD supervised the data collection and the conduct of follow-up; Wang T analyzed the data and was a major contributor in writing the manuscript; all authors read and approved the final manuscript.

**Supported by** National Natural Science Foundation of China, No. 81701058; Shandong Academy of Sciences, No. ZR2017PH027; and China Postdoctoral Science Foundation, No. 2017M612288.

**Corresponding author: Tan Wang, MD, PhD, Professor,** Department of Geriatrics, Qilu hospital of Shandong University, No. 107 West Wenhua Road, Jinan 250012, Shandong Province, China. olivelwang@sdu.edu.cn

**Received:** February 6, 2021

**Revised:** March 27, 2021

**Accepted:** May 17, 2021

**Published online:**

**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 (HP) and treatment with Prussian blue (PB). A 24-mo 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 including 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 was ineffective, while HP and treatment with PB 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-mo follow-up period.

CONCLUSION

Identification of incident cluster and characteristic symptoms is extremely important for early diagnosis of acute thallium poisoning. HP plus PB is essential to improve the prognosis of thallium-poisoned patients.

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

Wang TT, Wen B, Yu XN, Ji ZG, Sun YY, Li Y, Zhu SL, Cao YL, Wang M, Jian XD, Wang T. Early diagnosis, treatment, and outcomes of five patients with acute thallium poisoning. *World J Clin Cases* 2021; In press

**Core Tip:** Thallium poisoning is rare and easily to be misdiagnosed. In this study, dysesthesia of limbs, 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 d 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 summarized 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 was noted, and they received targeted therapies, including hemoperfusion (HP) and Prussian blue (PB). At the 24-mo follow-up, four (80%) patients 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-mo follow-up study after discharge, the symptoms were recorded at 1, 3, 12, and 24 mo, 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 at 12 mo.

**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) patients were from the same family, and the second (patient 2) and third (patient 3) patients 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, gastrointestinal symptoms including abdominalgia, loss of appetite, nausea, and vomiting progressively aggravated, and 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 (100%) patients 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 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 d of exposure. The patients underwent rapid detoxification treatment with sodium thiosulfate (3-11 d 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 d 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 2 wk. 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 at 1 mo, the 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. The 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-mo follow-up, the original symptoms of four (80%) patients markedly improved, except for patient 1, who developed blindness and dysphagia. At the 24-mo 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 mo 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-mo 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 d, which is much shorter than the typical interval of 23.6 d 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 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[21,22]. It was reported that the application of sodium diethyldithiocarbamate may cause redistribution of thallium into the central nervous system[23]. 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[24]. 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[9,10,25,26]. 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 5 d 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 an 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-mo follow-up.

***Research conclusions***

Identification of incident cluster and characteristic symptoms is 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 a control group to make the conclusions more reliable.

**ACKNOWLEDGEMENTS**

We would like to express our thanks to Hospital 307 of Chinese People’s Liberation Army for guidance of diagnosis and providing therapies to thallium poisoning, which were crucial to conduct our study.

**REFERENCES**

1 **Galván-Arzate S**, Santamaría A. Thallium toxicity. *Toxicol Lett* 1998; **99**: 1-13 [PMID: 9801025 DOI: 10.1016/s0378-4274(98)00126-x]

2 **Cvjetko P**, Cvjetko I, Pavlica M. Thallium toxicity in humans. *Arh Hig Rada Toksikol* 2010; **61**: 111-119 [PMID: 20338874 DOI: 10.2478/10004-1254-61-2010-1976]

3 **Lennartson A**. Toxic thallium. *Nat Chem* 2015; **7**: 610 [PMID: 26100812 DOI: 10.1038/nchem.2286]

4 **Galván-Arzate S**, Pedraza-Chaverrí J, Medina-Campos ON, Maldonado PD, Vázquez-Román B, Ríos C, Santamaría A. Delayed effects of thallium in the rat brain: regional changes in lipid peroxidation and behavioral markers, but moderate alterations in antioxidants, after a single administration. *Food Chem Toxicol* 2005; **43**: 1037-1045 [PMID: 15833379 DOI: 10.1016/j.fct.2005.02.006]

5 **Tsai YT**, Huang CC, Kuo HC, Wang HM, Shen WS, Shih TS, Chu NS. Central nervous system effects in acute thallium poisoning. *Neurotoxicology* 2006; **27**: 291-295 [PMID: 16337004 DOI: 10.1016/j.neuro.2005.10.009]

6 **Osorio-Rico L**, Santamaria A, Galván-Arzate S. Thallium Toxicity: General Issues, Neurological Symptoms, and Neurotoxic Mechanisms. *Adv Neurobiol* 2017; **18**: 345-353 [PMID: 28889276 DOI: 10.1007/978-3-319-60189-2\_17]

7 **Wang Q**, Huang X, Liu L. Analysis of nine cases of acute thallium poisoning. *J Huazhong Univ Sci Technolog Med Sci* 2007; **27**: 213-216 [PMID: 17497301 DOI: 10.1007/s11596-007-0229-4]

8 **Zhao G**, Ding M, Zhang B, Lv W, Yin H, Zhang L, Ying Z, Zhang Q. Clinical manifestations and management of acute thallium poisoning. *Eur Neurol* 2008; **60**: 292-297 [PMID: 18824857 DOI: 10.1159/000157883]

9 **Huang C**, Zhang X, Li G, Jiang Y, Wang Q, Tian R. A case of severe thallium poisoning successfully treated with hemoperfusion and continuous veno-venous hemofiltration. *Hum Exp Toxicol* 2014; **33**: 554-558 [PMID: 23900304 DOI: 10.1177/0960327113499039]

10 **Lin G**, Yuan L, Peng X, Long J, Wang C, Bai L, Lu X, Dong J, Liu Y, Wang Y, Qiu Z. Clinical characteristics and treatment of thallium poisoning in patients with delayed admission in China. *Medicine (Baltimore)* 2019; **98**: e16471 [PMID: 31335706 DOI: 10.1097/MD.0000000000016471]

11 **Li JM**, Wang W, Lei S, Zhao LL, Zhou D, Xiong H. Misdiagnosis and long-term outcome of 13 patients with acute thallium poisoning in China. *Clin Toxicol (Phila)* 2014; **52**: 181-186 [PMID: 24580057 DOI: 10.3109/15563650.2014.892123]

12 **Li S**, Huang W, Duan Y, Xing J, Zhou Y. Human fatality due to thallium poisoning: autopsy, microscopy, and mass spectrometry assays. *J Forensic Sci* 2015; **60**: 247-251 [PMID: 25407479 DOI: 10.1111/1556-4029.12623]

13 **Riyaz R**, Pandalai SL, Schwartz M, Kazzi ZN. A fatal case of thallium toxicity: challenges in management. *J Med Toxicol* 2013; **9**: 75-78 [PMID: 22865288 DOI: 10.1007/s13181-012-0251-1]

14 **Sun TW**, Xu QY, Zhang XJ, Wu Q, Liu ZS, Kan QC, Sun CY, Wang L. Management of thallium poisoning in patients with delayed hospital admission. *Clin Toxicol (Phila)* 2012; **50**: 65-69 [PMID: 22175787 DOI: 10.3109/15563650.2011.638926]

15 **Ratti F**, Facchini A, Beck E, Cazzaniga S, Francesconi S, Tedesco C, Terrani A, Ciceri G, Colombo R, Saini M, Petrolini VM, Citerio G. "Familial venoms": a thallium intoxication cluster. *Intensive Care Med* 2018; **44**: 2298-2299 [PMID: 30293149 DOI: 10.1007/s00134-018-5403-6]

16 **van Swieten JC**, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988; **19**: 604-607 [PMID: 3363593 DOI: 10.1161/01.str.19.5.604]

17 **Mulkey JP**, Oehme FW. A review of thallium toxicity. *Vet Hum Toxicol* 1993; **35**: 445-453 [PMID: 8249271]

18 **Peter AL**, Viraraghavan T. Thallium: a review of public health and environmental concerns. *Environ Int* 2005; **31**: 493-501 [PMID: 15788190 DOI: 10.1016/j.envint.2004.09.003]

19 **Moore D**, House I, Dixon A. Thallium poisoning. Diagnosis may be elusive but alopecia is the clue. *BMJ* 1993; **306**: 1527-1529 [PMID: 8518684 DOI: 10.1136/bmj.306.6891.1527]

20 **Yu V**, Juhász M, Chiang A, Atanaskova Mesinkovska N. Alopecia and Associated Toxic Agents: A Systematic Review. *Skin Appendage Disord* 2018; **4**: 245-260 [PMID: 30410891 DOI: 10.1159/000485749]

21 **Henderson P**, Hale TW, Shum S, Habersang RW. N-Acetylcysteine therapy of acute heavy metal poisoning in mice. *Vet Hum Toxicol* 1985; **27**: 522-525 [PMID: 4082467]

22 **Mulkey JP**, Oehme FW. Are 2,3-dimercapto-1-propanesulfonic acid or prussian blue beneficial in acute thallotoxicosis in rats? *Vet Hum Toxicol* 2000; **42**: 325-329 [PMID: 11111936]

23 **Kamerbeek HH**, Rauws AG, ten Ham M, van Heijst AN. Dangerous redistribution of thallium by treatment with sodium diethyldithiocarbamate. *Acta Med Scand* 1971; **189**: 149-154 [PMID: 5090197 DOI: 10.1111/j.0954-6820.1971.tb04356.x]

24 **Hoffman RS**. Thallium toxicity and the role of Prussian blue in therapy. *Toxicol Rev* 2003; **22**: 29-40 [PMID: 14579545 DOI: 10.2165/00139709-200322010-00004]

25 **Zhao J**, Peng X, Wang C, Bai L, Dong J, Lu X, Liu Y, Feng S, Long J, Qiu Z. [Efficacy analysis of prussian blue or its combination with hemoperfusion in the treatment of acute thallium poisoning]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2018; **30**: 695-698 [PMID: 30045801 DOI: 10.3760/cma.j.issn.2095-4352.2018.07.016]

26 **Lin G**, Yuan L, Bai L, Liu Y, Wang Y, Qiu Z. Successful treatment of a patient with severe thallium poisoning in a coma using Prussian blue and plasma exchange: A case report. *Medicine (Baltimore)* 2019; **98**: e14629 [PMID: 30813198 DOI: 10.1097/MD.0000000000014629]

27 **Misra UK**, Kalita J, Yadav RK, Ranjan P. Thallium poisoning: emphasis on early diagnosis and response to haemodialysis. *Postgrad Med J* 2003; **79**: 103-105 [PMID: 12612328 DOI: 10.1136/pmj.79.928.103]

28 **Tian YR**, Sun LL, Wang W, Du F, Song AX, Ni CY, Zhu Q, Wan Q. A case of acute thallotoxicosis successfully treated with double-filtration plasmapheresis. *Clin Neuropharmacol* 2005; **28**: 292-294 [PMID: 16340387 DOI: 10.1097/01.wnf.0000192137.46145.0d]

29 **Lu CI**, Huang CC, Chang YC, Tsai YT, Kuo HC, Chuang YH, Shih TS. Short-term thallium intoxication: dermatological findings correlated with thallium concentration. *Arch Dermatol* 2007; **143**: 93-98 [PMID: 17224548 DOI: 10.1001/archderm.143.1.93]

30 **Pelclová D**, Urban P, Ridzon P, Senholdová Z, Lukás E, Diblík P, Lacina L. Two-year follow-up of two patients after severe thallium intoxication. *Hum Exp Toxicol* 2009; **28**: 263-272 [PMID: 19755458 DOI: 10.1177/0960327109106487]

31 **Zhang HT**, Qiao BP, Liu BP, Zhao XG. Study on the treatment of acute thallium poisoning. *Am J Med Sci* 2014; **347**: 377-381 [PMID: 23811578 DOI: 10.1097/MAJ.0b013e318298de9c]

32 **Almassri I**, Sekkarie M. Cases of thallium intoxication in Syria: A diagnostic and a therapeutic challenge. *Avicenna J Med* 2018; **8**: 78-81 [PMID: 30090745 DOI: 10.4103/ajm.AJM\_17\_18]

33 **Ash RD**, He M. Details of a thallium poisoning case revealed by single hair analysis using laser ablation inductively coupled plasma mass spectrometry. *Forensic Sci Int* 2018; **292**: 224-231 [PMID: 30343235 DOI: 10.1016/j.forsciint.2018.10.002]

**Footnotes**

**Institutional review board statement:** The study was reviewed and approved by the Science and Research Office of Qilu Hospital of Shandong University.

**Informed consent statement:** All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

**Conflict-of-interest statement:** There are no conflicts of interest to report.

**Data sharing statement:** No additional data are available.

**STROBE statement:** The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Peer-review started:** February 6, 2021

**First decision:** March 25, 2021

**Article in press:**

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Stankiewicz R **S-Editor:** Fan JR **L-Editor:** Wang TQ **P-Editor:**

**Table 1 Clinical symptoms of five patients with acute thallium poisoning**

|  |  |  |  |
| --- | --- | --- | --- |
| **Patient No.** | **Age**  | **Initial symptoms** | **Accompanying symptoms** |
| **Hepatic damage** | **Alopecia** | **Coagulopathy** | **Central nervous symptoms** |
| 1 | 40 | Dysesthesia of distal limbs with hyperalgesia, weakness of lower limbs  | + | + (10th day) | + (11th day-16th day) | + (13th day) |
| 2 | 33 | Dysesthesia of lower limbs with hyperalgesia, lumbodynia | + | + (9th day) | - | - |
| 3 | 49 | Hypalgesia of two hands, abdominalgia | + | + (8th day) | + (11th day-13th day) | + (15th day) |
| 4 | 44 | Dysesthesia and paresthesia of lower limbs, abdominalgia, | + | + (8th day) | - | - |
| 5 | 37 | Dysesthesia, weakness, abdominalgia | + | + (3rd day) | - | + (12th day) |

The initial symptoms are the chief complaints of the patients at admission. The accompanying symptoms that we observed during hospitalization are recorded in the table. “+”: Symptoms were positive; “-“: Symptoms were negative. Date in parentheses was the occurrence time when the symptoms appeared after exposure.

**Table 2 Laboratory findings and electromyography results of five patients with acute thallium poisoning**

|  |  |  |
| --- | --- | --- |
| **Patient No.** | **Abnormal laboratory findings** | **EMG** |
| **ALT (u/L)** | **CK-MB (u/L)** | **APTT (s)** | **Motor nerve** | **Sensory nerve** |
| 1 | 117.8 | 28 | 163.1 (12th day) | La-Me (M) | La-Me (m) |
| 2 | 65.8 | Normal | Normal | Normal | Normal |
| 3 | 71.1 | 22.3 | 125.2 (12th day) | Normal | La-S (m) |
| 4 | 92.1 | 37 | Normal | Normal | Normal |
| 5 | 55.3 | Normal | Normal | Normal | Bi-Me (m) |

The values of abnormal lab findings at admission are listed in the table. The peak of activated partial thromboplastin time and the time of detection (after exposure) were recorded. Electromyography was performed before or at admission. Bi: Bilateral; La: Lateral; S: Sural nerve; Me: Median nerve; m: Mild-decreased conduction velocity (CV) or amplitude < 20%; M: Moderate-decreased CV or amplitude range from 20% to 50%; ALT: Alanine aminotransferase, ref: 0-50 u/L; CK-MB: Creatine kinase-MB, ref: 0-16 u/L; APTT: Activated partial thromboplastin time, ref: 23-35 s; Normal: Values within normal limits; EMG: Electromyography.

**Table 3 Interval from exposure to diagnosis and treatments of five patients with acute thallium poisoning**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Patient No.** | **Interval from exposure to diagnosis (d)** | **Time of receiving treatments after exposure** | **Duration of PB treatment (d)** | **Urine thallium concentration (µg/L)** | **Blood thallium concentration (µg/L)** |
| **Sodium thiosulfate** | **DMPS** | **HP** | **PB** | **Before treatment** | **After treatment** | **Before treatment** | **After treatment** |
| 1 | 9  | 3rd day | 12th day | 15th day | 15th day | 14 | 7200 | 160 | 280 | 0 |
| 2 | 8  | 3rd day | 10th day | 10th day | 11th day | 15 | 5100 | 130 | 210 | 0 |
| 3 | 11  | 10th day | 11th day | 15th day | 15th day | 15 | 250 | 0 | 150 | 0 |
| 4 | 12  | 11th day | 11th day | 15th day | 15th day | 14 | 370 | 0 | 40 | 0 |
| 5 | 12 | 11th day | 11th day | 15th day | 15th day | 16 | 580 | 0 | 46 | 0 |

The urine and blood samples were successively sent to Hospital 307 of Chinese People’s Liberation Army to confirm the diagnosis of acute thallium poisoning. The day when the patients underwent detoxification treatments after exposure is listed in the table. The Prussian blue (PB) treatment was implemented in Hospital 307 of Chinese People’s Liberation Army and lasted for 14 to 16 d. The urine and blood thallium concentration before and after PB treatment was recorded. Sodium thiosulfate: 0.64 g, intravenous injection per day; DMPS: Dimercaptopropane sulfonate 0.25 g, intramuscular injection twice daily; HP: Hemoperfusion; PB: Prussian blue 3.3 g in mannitol 50 mL, orally four times daily.

**Table 4 Symptoms of five patients with acute thallium poisoning during 24-mo follow-up**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Patient No.** | **1 mo** | **3 mo** | **12 mo** | **24 mo** |
| 1 | Bradypsychia, blepharoptosis, paresthesia of lower limbs, alopecia | Cognitive impairment, alopecia, nystagmus, hypalgesia of limbs | Blind, dysphagia | Blind, disability |
| 2 | Dysesthesia of fingers, alopecia | Hypalgesia of limbs, alopecia, bradypsychia | N/A | N/A |
| 3 | Dysesthesia of limbs, alopecia | Alopecia, palpitation | Fatiguability | N/A |
| 4 | Dysesthesia of lower limbs, alopecia | Alopecia | N/A | N/A |
| 5 | Dysesthesia of limbs alopecia, abdominalgia dysphasia | Weakness of lower limbs, alopecia, bradypsychia | N/A | N/A |

The clinical follow-up was performed at 1, 3, 12, and 24 mo after discharge. The main symptoms which may be associated with acute thallium poisoning are recorded in the table. N/A: No symptoms or complaints at all.

**Table 5 Examination results of five patients with acute thallium poisoning at 12-mo follow-up**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Patient number** | **EMG** | **MMSE** | **HAMA score** | **HAMD score** | **mRS** |
| **Motor nerve** | **Sensory nerve** |
| 1 | Bi-T (S) | Bi-T (M), Bi-S (M), Bi-Me (M) | 5 | - | - | 4 |
| 2 | Normal | Bi-S (m) | 29 | 5 | 3 | 0 |
| 3 | Normal | Bi-T (m), Bi-S (m), | 22 | 11 | 11 | 0 |
| 4 | Normal | Normal | 26 | 9 | 4 | 0 |
| 5 | Bi-U (m) | Bi-S (m), Bi-Me (m) | 27 | 4 | 3 | 0 |

The patients received electromyography, Mini-Mental State Examination, Hamilton Anxiety Rating Scale, Hamilton Depression Rating Scale, and Modified Rankin Scale assessments 12 mo after discharge. -: Unable to complete this test; Bi: Bilateral; La: Lateral; T: Tibial nerve; S: Sural nerve; Me: Median nerve; U: Ulnar nerve; m: Mild-decreased conduction velocity (CV) or amplitude < 20%; M: Moderate-decreased CV or amplitude range from 20% to 50%; S: Severe-decreased CV or amplitude > 50%; MMSE: Mini-Mental State Examination (ref: illiteracy > 17; primary school > 20; above middle school > 24); HAMA: Hamilton Anxiety Rating Scale (ref: normal < 7; probable anxiety 7-14; mild anxiety 14-21; moderate anxiety 21-29; severe anxiety > 29); HAMD: Hamilton Depression Rating Scale (ref: normal < 8; probable depression 8-20; depression 20-35; severe depression > 35); mRS: Modified Rankin Scale assessment (ref: 0, no symptoms at all; 4, Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance); EMG: Electromyography.

**Table 6 Intervals from exposure to diagnosis and outcomes from published studies on patients with thallium poisoning**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Number of cases** | **Mean interval from exposure to diagnosis (d)** | **Follow-up (mo)** | **Outcomes** |
| **Death** | **Survive with severe sequelae** | **Survive with mild sequelae** |
| Misra *et al*[27], 2003 | 1 | 18 | 6 | 0 | 0 | 1 |
| Tian *et al*[28], 2005 | 1 | 20 | During hospitalization | 0 | 0 | 1 |
| Lu *et al*[29], 2007 | 2 | 21 | 12 | 0 | 0 | 2 |
| Zhao *et al*[8], 2008 | 3 | 21.7 | 1-3 | 0 | 0 | 3 |
| Pelclová*et al*[30], 2009 | 2 | 112.5 | 18-22 | 0 | 2 | 0 |
| Sun *et al*[14], 2012 | 14 | 14.6 | 6-8 | 1 | 0 | 13 |
| Huang *et al*[9], 2014 | 1 | 2 | During hospitalization | 0 | 0 | 1 |
| Zhang *et al*[31], 2014 | 9 | 12.1 | 6 | 0 | 0 | 9 |
| Li *et al*[11], 2014 | 13 | 23.8 | 12-144 | 2 | 0 | 11 |
| Li *et al*[12], 2015 | 2 | 153 | During hospitalization | 2 | 0 | 0 |
| Almassri *et al*[32], 2018 | 3 | 45 | 20 | 0 | 0 | 3 |
| Ash andHe[33], 2018 | 1 | 150 | 37 | 0 | 1 | 0 |
| Lin *et al*[10], 2019 | 34 | 13 | 21-96 (31 cases) | 0 | 2 | 29 |
| Total | 86 | 23.6 | 1-144 | 5 | 5 | 73 |

The intervals from exposure of thallium to diagnosis were converted into days. One week = 7 d; One month = 30 d. The recent exposure was chosen for this study in the patients with multiple intoxications. Cases were grouped according to the outcomes described in the original papers: Death, severe sequelae (need assistance with daily activities), and mild sequelae (independent for daily activities).