

Clinical characteristics and treatment of thallium poisoning in patients with delayed admission in China

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Abstract

Thallium is highly toxic and its effects are cumulative. The clinical symptoms of thallium poisoning are non-specific, thereby delaying admission and treatment. This study aimed to summarize the clinical features and treatment experience of patients with delayed admission who experience thallium poisoning.

We conducted a retrospective descriptive analysis of patients in our hospital from 2008 to 2018 who had thallium poisoning and experienced a delay in hospital admission. The time from symptom onset to admission was assessed. The patients were divided into 3 groups and descriptive analyses of their clinical characteristics, including basic patient information, symptoms, laboratory test results, examination findings, treatment methods, outcomes, and follow-up information, were conducted.

A total of 34 patients with thallium poisoning were included: 8 were admitted to the hospital early or with mild delay, 9 had a moderate delay, and 17 had a severely delayed admission. The time from illness onset to admission was 13 (interquartile range, 7.5–26) days. Some patients with delayed admission had significant symptoms associated with central nervous system damage, and changes in magnetic resonance images and electroencephalograms were also noted. After admission, all patients received Prussian blue treatment, and some patients with relatively high blood concentration received blood purification treatments. Following treatment, the blood and urine thallium concentrations of all patients decreased significantly, and their symptoms were alleviated.

Our results show that delayed patient admission in cases of thallium poisoning is associated with greater risk of central nervous system damage. Use of Prussian blue combined with blood purification treatments might improve patients' conditions.

Abbreviations: EEG = electroencephalogram, EMG = electromyogram, IQR = interquartile range, MRI = magnetic resonance imaging, PB = Prussian blue.

Keywords: blood purification, delayed admission, poisoning, Prussian blue, thallium

1. Introduction

Thallium is an odorless, colorless, and rare heavy metal that occurs in nature, primarily in the form of oxides, halides,

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sulphates, carbonates, and acetate compounds.^[1] Thallium compounds have been widely used for rodenticides; however, due to cases of thallium poisoning, use of these compounds has been banned in many countries.^[2-4] Despite this, thallium poisoning persists in developing countries, including China, primarily as a result of criminal actions.^[5-7] Thallium salts are extensively absorbed through almost all routes of exposure. Oral bioavailability of hydrophilic thallium salts approaches 90% to 100%.^[1] Since thallium salts can be distributed in many organs of the human body, the symptoms of thallium poisoning are diverse and non-specific. Therefore, individuals who experience thallium poisoning are prone to a delayed admission. There is also a lack of evidence for effective treatment methods in patients whose admission was delayed. Thus, this study aimed to summarize the clinical features and treatment experience of patients with thallium poisoning and delayed admission.

2. Methods

2.1. Study design and setting

This retrospective, descriptive, single-center study was conducted at the Affiliated Hospital Academy of Military Medical Sciences (the Poisoning Treatment Center of the Army and National Key Clinical Specialties) and analyzed data of patients who were diagnosed with thallium poisoning between 2008 and 2018. Blood and urine thallium tests were performed by the poisondetection laboratory of our hospital and measured by atomic absorption spectrometry. All study participants provided informed consent, and the retrospective study design was approved by the appropriate ethics review board of our hospital.

2.2. Patient selection and grouping

Eligible participants included patients diagnosed with thallium poisoning in our department. Patients with chronic thallium poisoning and patients with other poisoning were excluded. To distinguish the clinical features of patients with different admission times and according to the stages of thallium poisoning,^[8] we divided patients into 3 groups according to the time from symptom onset to admission. Patients admitted to the hospital within 7 days were considered to have immediate admission or a mild delay in admission, and we classified this group of patients as early admission. The patients who presented between 7 and 14 days were categorized as moderate delay in admission, and the patients admitted after 14 days from symptom onset were categorized as severe delay in admission.

2.3. Data collection and variables

Data were obtained through the hospital case management office and included all patients with thallium poisoning within the specified research period. Variables were determined by QZW, WYA, and LGD; 2 doctors, BLL and LYQ, carefully reviewed the cases and collected case data. The follow-up data were obtained by telephone. Collected variables included the following:

- 1. Descriptive analyses of basic patient characteristics, including sex, age, the etiologies of poisoning, modes of exposure, time from onset to presentation, symptoms at admission, organ damage and blood and urine thallium concentrations at admission, laboratory findings, and EMG (electromyogram), MRI (magnetic resonance imaging), and EEG (electroencephalogram) findings;
- 2. treatment methods employed, including detailed descriptions of the Prussian blue (PB) and blood purification methods;
- 3. prognoses of patients, including changes in blood and urine thallium concentrations, symptoms at discharge;
- 4. follow-up data.

2.4. Statistical methods

Data analysis was performed using SPSS Statistics Software (version 20; IBM Corp., Armonk, NY). The Shapiro–Wilk test was used to test the normal distribution of numerical variables. Continuous variables were expressed as means with standard deviations or medians with the interquartile range (IQR), if the assumption of a normal distribution was violated. Categorical variables were given in numbers and percentages. Either the one-way ANOVA (with post-hoc least square differences method) or Kruskal–Wallis test (with post-hoc Dunn multiple comparison test) was used for 3-group comparisons of continuous variables. The Fisher exact test (with a Bonferroni correction for multiple comparisons) was used to analyze contingency tables with small sample sizes. A 2-sided *P* value of < .05 was considered significant.

3. Results

3.1. Baseline characteristics

A total of 34 patients with thallium poisoning were included in this study, and all patients were diagnosed in our department. Detailed patient information is summarized in Table 1. The mean and standard deviation of patient ages were 39.9 ± 13.2 years; 3 patients were under the age of 18. This study included 19 men (55.9%). Among the cohort, 8 were admitted early (23.5%), 9 (26.5%) experienced a moderate delay in admission, and 17 (50%) experienced a severe delay in admission.

The time from symptom onset to admission to our department was 13 days (IQR, 7.5-26). Of the 34 patients, 22 patients were poisoned through criminal activities, 11 patients had unexplained poisoning, and 1 patient was suicidal. All patients were poisoned by digestion. Three patients were admitted directly to our hospital and 18 were referred to a number of hospitals (none were clearly diagnosed, and all had been given symptomatic supportive treatment), with a median referral frequency of 2.5 (IQR, 1-3) times. Additionally, 13 patients were misdiagnosed with other diseases, including Guillain-Barre syndrome (50%), gastritis (41.7%), rheumatic immune disease (8.3%), skin disease (8.3%), and mental illness (8.3%). The initial symptom of 18 (52.9%) patients was abdominal pain, 12 (35.3%) patients had pain in extremities, and 4 (11.8%) patients had abdominal distension. In addition, due to the concealment of thallium poisoning, most patients were unable to determine the exact time of poisoning and the poisoning dose.

3.2. Clinical findings

3.2.1. Clinical symptoms. The patients' clinical findings are shown in Table 1. Patients with severe delayed admission had significantly lower blood and urinary concentrations at admission compared to those with early admission. The proportion of those who had abdominal pain symptoms on early admission was significantly higher compared to those with severe delayed admission, whereas the proportion of those with hair loss who experienced severe delayed admission was significantly greater. In terms of neurological symptoms, with the exception of 2 children and a patient with a severe coma, the other patients all developed pain in the extremities. Of all the patients, 2 developed difficulty urinating (catheterization was performed); 2 developed vulvar pains (excluding vulvitis); and 3 developed significant central nervous system damage on admission (one patient had memory loss; one patient had confusion; 1 patient was in a deep coma, and all the 3 patients experienced severe delayed admission).

3.2.2. Clinical examinations. There was no difference between those who experienced severe delayed admission and early admission in terms of all organ injuries; however, the proportion of those who experienced liver injury was the highest (50%) compared to other organ injuries. In addition, at admission, the majority of patients (26 patients, 76.5%) had a normal white blood cell count and 8 patients (26.5%) had an increase in white blood cell levels (10.12–22.24 \times 10⁹ cells/L). The results of the examinations of the nervous system were as follows. Eleven patients (32.4%) (2 early admission patients, 3 moderate delay admission patients and 6 severe delay admission patients) underwent cranial MRI. All patients were examined by MRI after admission, and the time of MRI was 14 (IQR, 10-44) days from onset. The results showed that 3 patients had obvious abnormal MRIs, all of whom experienced a severe delayed admission; 2 among them had central nervous system symptoms on admission (confusion and deep coma), and the other one was found to have a personality change during follow-up.

Five patients underwent EEG examination. One of them experienced a moderate delay in admission with a slightly

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Baseline and clinical characteristics of patients with thallium poisoning.

	All patients	Early admission	Moderate delay admission	Severe delay	
Characteristics	(n = 34)	(n = 8)	(n = 9)	admission (n=17)	Р
Demographic characteristics					
Male (%)	19 (55.9)	5 (62.5)	3 (33.3)	11 (64.7)	.21
Age (years) [†]	39.9 ± 13.2	42.0 ± 12.3	39.3 ± 13.3	35.2 ± 13.7	.46
Time from onset to admission (days)	13 (7.5-26)	5 (4-5)	10 (8.5–10)	25 (15-60)	NA
Initial blood/urine thallium concentration (ng/	mL)				
Blood thallium*	293 (65.6-742)	922 (402.3-1896.3)	450 (237-744)	85 (43–293.5) [‡]	.01
Urine thallium [*]	2500 (422-7407)	12159 (3032–18323)	5100 (715–7517)	595 (218.7–3423.3) [§]	.01
Organ injury (%)					
Liver injury	17 (50.0)	5 (62.5)	5 (55.6)	7 (41.2)	.81
Kidney injury	2 (5.9)	1 (12.5)	0	1 (5.9)	.28
Myocardial injury	3 (8.9)	0	1 (11.1)	2 (11.8)	.43
Hypoxemia	5 (14.7)	2 (25)	1 (11.1)	2 (11.8)	.43
Symptoms and signs at admission (%)					
Gastrointestinal					
Abdominal pain	12 (35.3)	7 (87.5)	3 (33.3)	3 (17.6) [†]	.03
Abdominal distension	9 (26.5)	1 (12.5)	4 (44.4)	4 (23.5)	.13
Nausea/Vomiting	1 (2.9)	0	1 (11.1)	0	.16
Neurological					
Pain in extremities	31 (91%)	8 (100)	9 (100)	14 (82.4)	.94
Numbness in extremities and reduced sensation to light touch	17 (50.0)	5 (62.5)	6 (66.7)	6 (35.3)	.81
Tremor in extremities	1 (2.9)	1 (12.5)	0	0	.14
Numbness of scalp	4 (11.8)	2 (25.0)	2 (22.2)	0	.93
Coma	1 (2.9)	0	0	1 (2.9)	.96
Hair loss	19 (55.9)	1 (12.5)	4 (44.4)	14 (82.4) [§]	.02

* Median (IQR).

 $^{+}$ Mean \pm SD.

* P: significant differences compared to the other 2 groups.

[§] significant difference compared to the early admission group.

abnormal EEG. Four experienced a severe delay on admission (3 showing a mild abnormality, one showing a moderate abnormality); and of these 4 patients, 3 had MRI lesions (mentioned above).

A total of 16 patients underwent EMG, including 8 who experienced a moderate delay in admission and 8 who experienced a severe delay in admission. Among all patients, 5 had no damage (4 with moderate delay admission, 1 with severe delay admission), and the rest had varying degrees of damage. Among the EMG results, the most serious results were those of a patient in a deep coma showing severe neurogenic damage in all limbs. Detailed EMG results are shown in Supplemental File 1, http://links.lww.com/MD/D126.

3.2.3. Treatment and patient outcomes. After admission, the treatments received by patients included stomach protection, acid suppression, circulation improvement, nerve nutrition, protection of vital organs, pain relief, and PB. The method of treatment and patient outcomes are presented in Table 2. The median blood thallium concentration of all patients treated with blood purification treatment was 696 (IQR, 293.5–1098.3) ng/ml. Among the early admission patients, seven were given a blood purification treatment based on PB and symptomatic supportive therapy, and the blood thallium concentration of these patients at admission was 1009 (IQR, 649–1981) ng/ml. Among the patients who had a moderate delay in admission, 6 were given blood

Treatment methods and outcomes of patients with thallium poisoning.

	All patients (n=34)	Early admission (n=8)	Moderate delay admission (n=9)	Severe delay admission (n=17)
Blood purification methods				
PB alone (n)	16	1	3	12
PB+HP (n)	12	3	5	4
PB+PE (n)	1	0	0	1
PB+CRRT (n)	1	1	0	0
PB+HP+PE (n)	4	3	1	0
Outcomes Thallium concentration at discharge				
Blood thallium concentration (ng/ml)	25.1 (2.25–112.5)	73.5 (23.0–131.0)	39 (8.6–192.6)	10.1 (0-52.2)
Urine thallium concentration (ng/ml)	105 (22.8–540.5)	531 (144–621.5)	130 (55–477.4)	29.2 (2.5-393.5)
Hospital stay (days)	24.7 ± 12.3	25.1 ± 7.3	26.0 ± 6.3	23.8±16.4

CRRT = continuous renal replacement therapy, HP = hemoperfusion, PB = Prussian blue, PE = plasma exchange.

purification treatments based on PB and symptomatic supportive therapy, and the average blood thallium concentration of these patients at admission was 696 (IQR, 250.5–902.5) ng/ml. Among those who had a severe delay in admission, 5 patients were treated with blood purification based on PB and symptomatic supportive therapy, and 12 patients were treated with Prussian blue alone; the median blood thallium concentration of these patients at admission was 300 (IQR, 289–762.3) ng/ml and 19.7 (IQR, 2.6–108.3) ng/ml respectively. Details on the PB treatment method and blood purification are summarized in Supplemental File 2, http://links.lww.com/MD/D126.

None of the patients in this study died after treatment. The total length of hospital stay was 24.7 ± 12.3 days. The blood and urine thallium concentrations of all patients significantly reduced after both treatments, as shown in Table 2. In addition, all patients experienced improvement in symptoms and organ function following treatment.

3.2.4. Follow-up. Overall, 31 patients (91.2%) were followed up; the median follow-up time was 41 (IQR, 21–96) months. A total of 26 patients (83.9%) recovered well without any sequelae, and 5 of the patients had significant sequelae. Of these 5 patients, 2 who had a moderate delay in admission still had mild pain and numbness in the lower extremities at the time of follow-up. Among the other 3 patients, 1 person developed a personality change, and the patient who was in a deep coma could communicate normally after being treated in our hospital; however, that patient could not stand independently at the time of follow-up. The patient with confusion, due to early discharge, eventually suffered serious sequelae including ataxia, optic nerve damage, and respiratory muscle weakness. All 31 patients grew new hair 1 to 2 months after discharge.

4. Discussion

Thallium compounds can accumulate in the human body and be rapidly distributed throughout it, including in the skin and hair.^[1,9] The common symptoms of thallium poisoning include gastroenteritis, peripheral neuropathy, and hair loss.^[2,9–11] Due to complex multi-organ involvement, the symptoms of thallium poisoning are diverse and non-specific; therefore, early diagnosis is difficult, and delays in admission are common. Similar to previous research,^[3,4] most of the patients in this study had a delayed admission; specifically, the proportion of those with a severe delay (>14 days) in admission was the largest (median: 25 days), indicating that delayed admission after thallium poisoning remains a serious issue. In contrast to previous studies, we grouped patients according to time from onset of symptoms to hospital admission; a previous study classified thallium poisoning into immediate phase (within hours), intermediate phase (from hours to days), and late phase/residual phase (after 2 weeks).^[8] Grouping helped us to better understand the clinical characteristics of patients at different stages, especially those who had a severe delay in admission.

According to the literature,^[1,10,11] gastrointestinal symptoms such as abdominal pain occur soon after poisoning, while hair loss might occur 2 to 3 weeks after poisoning.^[1,7,12] In this study, those who were admitted early had significantly more symptoms associated with abdominal pain and less hair loss than those who had a delay in admission, indicating that most of the early admission patients were still in the early stage of poisoning; these differences in symptoms might help to judge a patient's time of

poisoning. In our study, those who had a delay in admission had lower blood thallium concentrations, and this might be due to the fact that the thallium ions absorbed into the body had been redistributed from the blood circulation to various tissues due to the longer poisoning time. Thallium poisoning can cause damage to multiple organs, especially to the liver, kidneys, and heart.^[1,10] Liver, kidney, and heart damage all occurred in patients in this study, with the largest proportion (50%) experiencing liver damage. However, the damage to patients' organs in all cases was not serious, and quickly alleviated after protective organ treatment. In addition, most patients in the present study had normal levels of white blood cells, with only 8 patients showing an increase. Progressive peripheral neuropathies develop into severe painful sensations 2 to 5 days after exposure^[1]; in our study, pain in the extremities occurred in almost all patients. However, because of the lack of systematic pain grading, it was not possible to understand the severity of peripheral neurological symptoms in patients in different groups. Analysis of 16 patients who had a moderate or severe delay in admission and who underwent EMG testing found that most patients with delayed admission had neurogenic damage, indicating that a delay in admission might be associated with serious peripheral nervous system damage. In addition, 3 of the patients who had a severe delay in admission developed central nervous system damage (experiencing symptoms such as memory loss, confusion, and even a deep coma); MRI results and EEGs indicated that injury occurred only in those who had a severe delay in admission. Furthermore, the follow-up results showed that there were no sequelae in those who had an early admission, while some patients who had a delay in admission suffered obvious nervous system sequelae. These results suggest that delayed admission is associated with a high probability of central nervous system injury.

Treatment for thallium poisoning consists of removal from exposure, supportive care, and enhanced elimination.^[10] For years, PB has been the most commonly prescribed antidote to treat this poisoning because it interrupts re-adsorption of thallium in the intestine and increases its elimination from the body.^[1,10,13] However, its availability is limited in many regions. In China, only a few research institutions have PB reserves. In addition to PB treatment, many studies have reported that blood purification is also an important treatment option.^[3,4,6,10,11,14,15] Although studies have shown that blood purification has a low clearance rate of thallium salt, it is still superior to other current removal methods and is therefore recommended for the treatment of thallium poisoning, especially severe thallium poisoning.^[10] Many experts have reached a consensus that the earlier that blood purification begins, the better the patient outcomes will be. It is best to start within 24 to 48 hours, and blood purification is recommended when blood thallium concentration is >0.4 mg/ L.^[10] Some scholars believe that even patients admitted to hospital later than 48 hours should be given blood purification treatment, but no consensus has been reached.^[10] A study showed that PB combined with hemodialysis is helpful in treating patients with delayed admission thallium poisoning.^[4] One thallium poisoning case report showed that the condition of a patient who was poisoned for 3 weeks had improved after hemodialysis treatment.^[15] Our research supports the existing studies of the efficiency of blood purification for treating those with delayed admission for thallium poisoning. In this study, all patients with relatively high blood thallium concentrations after admission (696; IQR, 293.5-1098.3 ng/ml) were given a blood purification treatment based on PB treatment. This treatment was given even for those who had a severe delay in hospital admission; the median blood thallium concentration of those patients was 300 (IQR, 289–762.3) ng/ml. After treatments, the condition of all patients greatly improved, and blood thallium concentrations gradually decreased, demonstrating that the treatments used were effective. Further research is needed on the criteria for blood purification, especially for those with a delay in hospital admission. The 3 children in this study were treated with PB alone, due to their age. Their blood and urine thallium concentrations decreased significantly, and the symptoms were generally relieved. However, this is still insufficient evidence for blood purification efficacy, as we did not have a parallel control patient group.

There are some limitations of this study. First, this was a retrospective descriptive analysis of a small patient sample, and the level of argumentation was low. Second, since most patients had delayed diagnoses, it was impossible to assess the clinical features of the early stage of thallium poisoning, and we were unable to collect the dose-response data. Third, there was no control group; therefore, the efficacy of blood purification therapy could not be determined.

In conclusion, the clinical manifestations of thallium poisoning are diverse and non-specific. In addition, this condition is prone to misdiagnosis and delayed treatment. Patients who experience a delay in admission are more prone to serious peripheral nervous system and central nervous system injury. In this study, PB combined with blood purification treatment was associated with the improvement of all patients' condition, even those who experienced a severe delay in admission.

Author contributions

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