



Diagnosis and treatment of persons with acute thallium poisoning

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ABSTRACT

Objective: This study aimed to describe organs and systems damages in persons after mass poisoning with thallium and show the results of treatment.

Methods: Forty-four persons (12 males and 32 females) with acute oral thallium poisoning were tested for thallium levels in blood and urine and examined by a toxicologist and a neurologist, and in some –cases, by a gynecologist, an ophthalmologist, and a psychiatrist. Persons were divided into the following three groups depending on the severity of the poisoning: I: This group consisted of 9 persons (blood thallium level 8.3–26.7 µg/L) and treatment applied in the hospital included intestinal lavage, antidote therapy with potassium-ferric hexacyanoferrate, sodium dimercaptopropanesulfonate; II: This group consisted of 21 persons (0.3–6.1 µg/L) who received a similar treatment at home; and III: This group consisted of 14 (normal) persons who did not receive any treatment.

Results: The most common combination of several symptoms such as alopecia (on day 17–23), muscle pain of different localization in the debut of the disease (>88.9 % of the persons), sudden unexplained general weakness (>76.2 % of the persons), peripheral paraparesis or tetraparesis (including no complaints), polyneuropathy (88.89 % in group I vs. 54.14 % in group II, $p < 0.05$), static and dynamic ataxia (33.3 % in group I vs. 19.4 % in group II, $p < 0.05$), vertigo (1/3 of the persons), postural tremor (1/3 of the persons), and cognitive and emotional disorders (2/3 of the persons). Ovarian dysfunction was observed in all women of group I but in 42.9 % of group II, $p < 0.05$. The treatment was successful. In group I, plasma and urine thallium level significantly decreased by 69.3 % and 84 %, respectively. Pain, movement and coordination disorders regressed first while tremor, sensory, cognitive and emotional disorders lasted longer. Polyneuropathies later became mono-neuropathies. Tremor could increase despite a decreased thallium concentration.

Discussion: The Sklifosovsky Institute conducted the largest study in Russian Federation investigating disorders in persons with acute thallium poisoning confirmed by laboratory tests. The clinical symptoms were consistent with those reported in the literature. The applied treatment was successful and led to better results compared to our previous approaches of treating mass thallium poisoning.

Conclusions: This study shows a typical combination of thallium poisoning symptoms and allows us to recommend a complex therapy without the use of extracorporeal detoxification methods.

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1. Introduction

Scientific publications and reports regularly describe cases of thallium poisoning in different countries; however, diagnosis is established only if most of clinical symptoms are present. Therefore, injured persons receive the necessary treatment late when poisoning effects may become irreversible. Thallium is a highly hazardous heavy metal used in light and heavy industry [1,2]. Since it is a colorless, water soluble, tasteless and affordable element, it may cause isolated and massive human poisoning [3]. In industry, poisoning occurs when security measures are not followed. The chemical and physical properties of the element allow its use for criminal purposes [4,5]. According to the literature, the lethal dose for oral administration is 10–15 mg/kg [6], however, in clinical practice, this is usually unknown.

The first symptoms of poisoning can be varying and non-specific, making differential diagnosis difficult. In case of incorrect diagnosis, poisoned people are treated for various gastrointestinal, gynecological, surgical, neurological diseases and muscle pain of different localization which complicates the situation and can lead to an unfavorable outcome [7,8]. As a main symptom of thallium poisoning, alopecia occurs only on day 10–14 of poisoning and forces the injured persons to contact a toxicologist [9,10]. The mechanism of action and pathogenesis has neurotoxic, enterotoxic, and nephrotoxic nature and involves impaired keratin formation in the hair follicles. Removal of poison occurs through the kidneys and intestines.

The literature describes isolated cases of thallium poisoning [3, 10–13]. It is difficult to form a unified idea of presentations of thallium poisoning. There are no scientific studies with a large number of persons, because there are few cases of mass poisonings. As a rule, when mass poisoning happens, injured persons are not comparable in age, invasion route of poison, poisoning severity, or blood and urine thallium levels. Thus, it is necessary to systematize the various symptoms of thallium poisoning.

There is no consensus of experts about the efficacy of various treatment strategies in thallium poisoning, such as hemodialysis, enterosorption and antidote therapy [9,10,12,13]. According to the literature, hemodialysis promotes rapid elimination of thallium from the body. The method is used for moderate and severe poisoning. In clinical toxicology, the consensus is that enteral detoxification is effective. It includes intestinal lavage and enterosorption which involves the use of a non-specific enterosorbent (activated carbon). Enteral saline solutions are used for intestinal lavage. Difficult question of choice is antidote therapy. In Russian Federation, sodium dimercaptopropanesulfonate (Unithiol) is used as an antidote in clinical practice for the treatment of any acute poisoning. Data on the use of specific potassium–ferric hexacyanoferrate (Ferrocin) as an antidote in Russian Federation is scarce. Ferrocin was used in isolated cases (no more than 2–3) without further evaluation of its efficacy [13,14]. The antidote therapy also includes oral administration of a 3–5% solution of sodium or potassium iodide. The purpose of using these drugs is formation of poorly soluble iodide compounds of thallium, which results in dramatic slowdown of its absorption in the intestine [7,14].

The last mass poisoning with thallium in the territory of the Russian Federation happened in the city of Taganrog. Poisoned people were referred to the N.V. Sklifosovsky Research Institute for Emergency Medicine (Moscow, Russian Federation) for examination and treatment.

A study investigating clinical symptoms of thallium poisoning in details has been performed and description the features of damage to organs and systems in persons with acute thallium poisoning and to show the results of treatment.

2. Materials and methods

Forty-four persons (12 males and 32 females) were admitted to the Toxicological Center of the Sklifosovsky Institute with acute thallium poisoning through about 69 (66; 75) days from the onset of the first

symptoms. They could not provide exact data on the cause of the poisoning and element invasion route into the body. All the poisoned people were working at the same factory in different offices, but their professional activity was not associated with thallium. All persons drank water from an office bottle, so an oral route was considered for the intake of the toxicant with drinking water. Blood and urine samples were taken from all persons to determine thallium level. The thallium level was determined by mass spectrometry. Thallium level was increased above normal ($<1 \mu\text{g/L}$ in blood and urine, 5–10 ng/g in human hair [15]) in 30 people who were included in the present work. The age of the persons was 37 (33; 43) years, 5 males and 25 females. There were no differences in person demographics. All persons were examined by a toxicologist ($n = 30$) and a neurologist ($n = 30$). Some persons were additionally examined by a gynecologist ($n = 20$), an ophthalmologist ($n = 7$), and a psychiatrist ($n = 14$). Blood and urine samples were taken from all persons for blood count, blood chemistry, coagulation profile, and urinalysis. For some persons ($n = 10$) data on the content of thallium in the hair and electroneuromyography ($n = 8$) was available. These studies were performed at the place of residence before contact to the Sklifosovsky Institute. Persons were referred to the Helmholtz National Medical Research Center of Eye Diseases (Moscow, Russian Federation) for consultation with an ophthalmologist. After treatment, persons were re-tested for thallium levels in blood and urine.

The persons were admitted to the poison control center, and an analysis of the thallium content in the hair was performed. In the presence of obvious clinical poisoning symptoms, the results of this analysis were negative. It should be noted that the analysis of thallium content in acute poisoning can be performed in the blood and urine, and in the hair – no earlier than 7 days after exposure. It is important to properly collect biosamples.

All persons ($n = 44$) were divided into three groups depending on the severity of the poisoning. There are no clear criteria for determination of severity by thallium level. Persons were assigned to different groups according to a combination of poisoning signs, blood and urine thallium levels, and clinical symptoms. The first group included 9 persons (3 males and 6 females) who had thallium levels significantly higher than normal (ranged from 8.3 to 26.7 $\mu\text{g/L}$ in blood and from 48.7 to 356.1 $\mu\text{g/L}$ in urine). Their condition was assessed as moderate according to complex of examinations. Hospitalization was offered for all persons of the first group, but 2 people refused treatment. Therefore, 7 persons were treated in the hospital. The second group included 21 persons (2 males and 19 females) with blood thallium level varied from 0.3–6.1 $\mu\text{g/L}$ in blood and from 2.8–68.5 $\mu\text{g/L}$ in urine who were offered treatment at home. The third group consisted of 14 persons (7 males and 7 females) with no poisoning signs at the time of the examination, who had thallium concentration within the normal range and were not included in the study.

In the first group ($n = 7$), the complex of therapeutic measures included intestinal lavage on the first and second day of hospitalization using 4.5 L of enteral saline solution. On the following day, antidote therapy using potassium-ferric hexacyanoferrate (Ferrocin) was done orally for 10 days at a daily dose of 3 g in combination with laxative preparations. After a 10-day course of ferrocin therapy, another intestinal lavage session was performed. During the entire period of in-patient treatment, all subjects received daily intramuscular injections of 5 mL of sodium dimercaptopropanesulfonate 5%. For correction of neurological disorders, the subjects were prescribed with B vitamins, alpha-lipoic acid preparations, microcirculation preparations and anticholinesterase drugs. The duration of in-patient treatment ranged from 9 to 18 days. In the second group, persons did not need in-patient treatment and were recommended treatment at home in a similar way, including ferrocin.

Persons received a second consultation by a toxicologist and a neurologist in dynamics after 53 (51; 55) days from the first appeal.

Data were expressed as median [interquartile range] or number (percentages). Mann–Whitney test was used. The threshold for statistical

significance was set at $p < 0.05$.

3. Results

On the primary consultation by a neurologist and a toxicologist, persons of the first and second groups complained of pain with different localization (88.89 vs. 100 %, respectively), general weakness and fatigue (88.89 vs. 76.2 %), impaired concentration (88.89 vs. 76.2 %). There were no statistically significant differences between the groups (Table 1) in terms of the above-noted conditions. Complaints of chest pain aggravated by inspiration, pain in the legs, mainly in the hips, were particularly common.

Persons of the first group more often complained of movement disorders (22.22 vs. 14.28 %, $p > 0.05$), sensitivity disorders (88.89 vs. 57.14 %, $p < 0.05$), tremor (22.22 vs. 19.04 %, $p > 0.05$), vertigo (33.3 vs. 28.6 %, $p > 0.05$), impaired walking (33.3 vs. 19.4 %, $p < 0.05$). Persons of the second group more often complained of emotional disorders (66.67 % vs. 55.56 %, $p < 0.05$). This pattern required a deeper study since the persons in the second group met the criteria of mild poisoning. It is necessary to accept the fact that all persons after poisoning communicated with each other and contributed to the induction of negative emotions. The people themselves reported that the office team was in an emotionally difficult situation of mass disease. In addition, all the persons of the first and second groups noted that they had difficulties with the usual work with documents, it became difficult to focus on current tasks, the concentration of attention was disturbed. The situation produced concerns because the persons had higher education as they were qualified lawyers, economists, accountants. If persons had serious neurological disorders, then complaints of emotional disorders faded into the background. To assess the psycho-emotional disorders, persons additionally completed a survey on the Hospital Anxiety and Depression Scale (HADS). Fourteen persons took part in the survey, 7 of them in the first group and 7 in the second group. According to the results of the study, psycho-emotional disorders were more often observed in persons of the second group compared to the first group (71.4 % vs. 57.1 %, respectively) and they presented more severe forms. For example, both clinical anxiety (57.1 vs. 42.9 %, $p > 0.05$) and clinical depression (28.6 vs. 14.3 %, $p > 0.05$) were more common in persons of the second group. Depression in all cases was accompanied by

Table 1

The ratio of complaints and objective examination data in persons with thallium poisoning of varying severity.

	I group (moderate severity), n = 9		II group (mild severity), n = 21	
	complaints	objective examination	complaints	objective examination
Pain of different localization	8 (88.89 %)	–	21 (100 %)	–
General weakness	8 (88.89 %)	–	16 (76.2 %)	–
Concentration disturbance	8 (88.89 %)	–	16 (76.2 %)	–
Emotional disorders	5 (55.56 %)	–	14 (66.67 %)	–
Movement disorders	2 (22.22 %)	5 (55.56 %)	3 (14.28 %)	7 (33.33 %)
Sensitive disorders	8 (88.89 %)	5 (55.56 %)	12 (57.14 %)	11 (52.38 %)
Tremor	2 (22.22 %)	4 (44.44 %)	4 (19.04 %)	5 (23.8 %)
Vertigo	3 (33.33 %)	–	6 (28.6 %)	–
Impaired walking	3 (33.33 %)	5 (55.56 %)	4 (19.04 %)	14 (66.67 %)
Visual impairment	5 (55.56 %)	4 (44.44 %)	15 (71.4 %)	7 (33.33 %)
Menstrual disorders	6 (66.67 %)	–	7 (33.33 %)	–

signs of anxiety. The results of the survey showed an inverse correlation between the severity of anxiety and depressive symptoms and the level of thallium in the blood and urine. Data on the HADS score in combination with analysis of the clinical manifestations of poisoning, indicated the dominant role of exogenous toxicosis in the formation of asthenic/astheno-depressive symptoms in subjects with thallium poisoning.

Complaints of persons with acute thallium poisoning did not always correspond to a physical examination. In persons of the first and second groups in the absence of complaints a motor neurological deficit was detected during the physical examination up to 2.5 times often (Table 1). This confirms the need for a detailed neurological examination of all people after thallium poisoning. When evaluating sensory disorders, persons more often complained, but there were no objective abnormalities (88.89 vs. 55.56 %, $p < 0.05$). We explain this observation with the fact that the persons not only had symptoms of loss of sensitivity (hypoesthesia), but also presented irritation symptoms (hyperesthesia/paresthesia). These disorders cannot be objectively identified. In persons of the first group, symptoms of increased, distorted sensitivity prevailed, sometimes in the form of pain and burning. In persons of the second group complaints of sensitive disorders coincided with physical examination data (57.14 vs. 52.38 %, $p > 0.05$). In this group of persons, symptoms of loss of sensitivity, such as hypoesthesia, prevailed.

The same discrepancy between complaints and physical examination was observed when the function of the cranial nerves was assessed. Most often, persons noted a decrease in visual acuity, photophobia, diplopia. This discrepancy was largely observed in persons of the second group. Persons complained of disorders of view 2 times more often than doctors found objective changes (71.4 vs. 33.3 %, respectively, $p < 0.05$). To clarify the pathology of eyes, persons were referred for consultation to an ophthalmologist. In persons of the first group, this discrepancy was insignificant (55.56 vs. 44.44 %, $p > 0.05$). Perhaps the current trends were also associated with the presence of psycho-emotional disorders in persons of the second group.

Women who complained of symptoms of reproductive system disorders, were referred for consultation to the gynecologist. To standardize the data, 20 persons were surveyed. Disruption of the menstrual cycle of different severity was reported by 6 women of the first group and 7 women of the second group. A questionnaire compiled by us was used to standardize data on the reproductive health of the persons. The survey involved 20 out of the 25 applicants. Of all those who participated in the survey, 6 persons were from the first group, 14 persons to the second one. Also, 17 (85 %) women had history of pregnancies, 16 (80 %) of childbirth, and 9 (45 %) of abortion. Gynecological diseases before thallium poisoning were diagnosed in 16 (80 %) women (uterine fibroids in 7, salpingo-oophoritis in 4, ovarian cyst in 2, adenomyosis in 2, and cervical erosion in 1). Menstrual cycle disorders before poisoning were reported by 7 (35 %) women, and 7 (35 %) persons took combined oral contraceptives prior to thallium poisoning.

More than half of women (12 (60 %) out of 20) reported menstrual irregularities secondary to thallium poisoning, while ovarian dysfunction was observed in all 6 (100 %) patients in group 1 and in 6 (42.9 %) persons in group 2. Every third persons (6 (30 %) out of 20) complained of an increased breast size, breast compaction and tenderness. Among the subjects of the first group, the described complaints were noted by one person while this number reached 5 in the second group.

When analyzing the available literature, we did not find publications on group poisoning of women of reproductive age, therefore, there is no similar study to compare our data with.

Alopecia in persons developed on the 17th–23rd day of the disease.

The period of in-patient treatment ranged from 9 to 18 days. In hospitalized persons, after the treatment complex, the plasma thallium concentration ranged from 1.6–9.1 µg/L. The thallium level showed a 3.9-time decrease until discharge (a decrease by 69.3 %). The urine thallium concentration ranged from 9.3 to 59.8 µg/L and the thallium

level had a 6.2-time decrease (by 84 %) until discharge. Subjects of the first group were discharged for home treatment, they subjectively noted improvement in their state of health. Persons of the second group were treated at home, re-examined and noted a gradual improvement in their condition. The residual effects of motor, sensory, coordinator, emotional and cognitive disorders remained objectively. Polyneuropathies became mononeuropathies with mild pain. Some persons reported regression of tremor, but there were some persons increased tremor. Persons reported a regression of pain, partial improvement of vision, normalization of the menstrual cycle, reduction in the intensity of hair loss.

4. Discussion

The Sklifosovsky Institute conducted the largest in Russian Federation study investigating the disorders in persons with acute thallium poisoning confirmed by laboratory tests. For the first time, in this study, the persons were comparable in the way the poison entered the body, the duration and severity of the poisoning, and age.

Persons with thallium poisoning in the debut of the disease complained of muscle pains of various localization and intensity. More than 80 % of the persons reported a sudden unexplained general weakness and quick fatigue combined with concentration and memory impairment. Also, 2/3 of the subjects suffered from emotional disorders and 67 % of the subjects had polyneuropathy. Vertigo was noted by every third person. Complaints did not always coincide with the physical examination data. For example, complaints of shakiness and gait disturbance were presented only by 25 % of the persons, and objectively static and dynamic ataxia was detected in 75 % of the persons. The weakness of a certain muscle group was noted by no more than 20 % of persons, but objectively, movement disorders in the form of peripheral paresis of varying severity (often lower paraparesis) were recorded in every second person. Only 20 % of the persons complained of trembling in their hands, but every third person was objectively registered with postural tremor of the fingers. In more than 1/3 of the persons, dysfunction of the cranial nerves (mainly 2 pairs) was detected by physical examination.

Emotional disorders of varying severity from subclinical forms of anxiety and depressive manifestations to developed asthenic-depressive and anxious-depressive states, were determined in persons. Certain difficulties arose when trying to clarify the pathogenesis of psycho-emotional disorders. These disorders could be manifestations of asthenic, astheno-depressive syndrome as a response to acute chemical trauma – neurotoxic, enterotoxic, nephrotoxic effect, hemodynamic disorders, hypoxia, metabolic disorders or mental disorders developed in response to a stressful situation as a fact of awareness of the disease. At that, the identity of the persons before the poisoning and the particular response to the illness/stressful situation were of great importance.

The persons worked in the same office, communicated closely with each other, and could help to induce some symptoms in their colleagues.

We concluded that the clinical symptoms of acute thallium poisoning were consistent with the literature data [16–18]. We supplemented them and confirmed by the results of laboratory studies. Persons sought medical advice late and, therefore, the diagnosis and treatment were also carried out late. The condition of the persons did not require intensive care or hemodialysis. The complex of therapeutic measures included specific antidote therapy (sodium dimercaptopropanesulfonate and ferrocen), intestinal lavage and symptomatic therapy. The treatment was successful. Subjects' well-being improved. Plasma and urine thallium level significantly decreased in groups I by 69.3 and by 84 %, respectively. This result is better than our previous result of treating mass thallium poisoning. Last time the urine thallium concentration decreased by 51.5 % without the use of hemodialysis or ferrocen and by 51.2 % when hemodialysis was included in the complex therapy, but without the inclusion of ferrocen. The obtained results allow us to recommend the complex therapy used in our study for moderate thallium poisoning without the use of extracorporeal detoxification

methods.

It is necessary to create a protocol (algorithm) for managing persons with thallium poisoning with a clear definition of the circle of specialists (including a neurologist) and a list of laboratory and instrumental diagnostics (including electroneuromyography). Special attention should be paid to cognitive and emotional disorders in persons with thallium poisoning. Persons need psychological rehabilitation. In the literature, there are no follow-ups for thallium poisoning. The question of the reversibility of events and the timing of possible disability of the person is still open. The study continues to the present, it is planned to maintain the connection of doctors with persons until a complete regression of the disorders.

5. Conclusions

An informative diagnostic test for acute thallium poisoning is the determination of the element in the blood and urine. The thallium concentration in the hair is determined later to establish the period of poisoning.

The combination of symptoms such as alopecia, muscle pain of different localization (mainly in the chest, in the proximal legs), peripheral paraparesis or tetraparesis, polyneuropathy (paresthesia and hyperesthesia), static and dynamic ataxia, postural tremor should raise suspicion of thallium poisoning. Persons with acute thallium poisoning have cognitive and severe emotional disorders; therefore, it is necessary to use psycho-emotional scales and consult a psychiatrist.

In thallium poisoning, pain, movement and coordination disorders regress first, while tremor, sensory, cognitive and emotional disorders last longer. Polyneuropathies later become mononeuropathies. Tremor may increase, despite decreases in thallium concentration.

The results of the present study allow us to recommend the complex therapy used in our observation for moderate thallium poisoning without the use of extracorporeal detoxification methods.

Persons with thallium poisoning need long-term follow-up by a neurologist and rehabilitation.

It is necessary to create a protocol for managing persons after thallium poisoning.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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