

Brief communication

Central nervous system effects in acute thallium poisoning

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Abstract

We report the central nervous system manifestations, neuropsychological studies and brain magnetic resonance image (MRI) findings of two patients with acute thallium intoxication. Neurologically the patients suffered from confusion, disorientation, and hallucination in the acute stage, followed by anxiety, depression, lack of attention, and memory impairment, in addition to peripheral neuropathy. Neuropsychological tests revealed an impairment of memory function, including reversed digital span, memory registration, memory recall, memory recognition, similarity, proverb reasoning, and verbal fluency. High concentrations of thallium were found in the urine, blood, and drinking water of these two patients. Brain MRI showed lesions in the corpus striatum in one patient. During the follow-up periods, the clinical manifestations and neuropsychological studies showed a slowly progressive improvement, and a follow-up brain MRI 1.5 months later demonstrated a resolution of the lesions.

We conclude that thallium intoxication might induce encephalopathy, and brain MRI studies demonstrated the acute-stage brain lesions in a severe intoxicated patient. In addition, neuropsychological tests also confirmed memory deficits, although the brain lesions in the corpus striatum might resolve.

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1. Introduction

Thallium, discovered by William Crookes in 1861, is a well-known heavy metal toxic to humans and animals. Thallium salts have been used for the treatment of many diseases, including tuberculosis, gonorrhea, syphilis, and fungal infections on the scalp. In addition, thallium has been used as a depilatory agent, and has had many victims, particularly among children, due to ingestion (Galvan-Arzate and Santamaria, 1998; Prick, 1979; Van Kesteren, 1994). An outbreak of thallositosis was reported in California in 1932, and was attributed to use of a rodenticide for the control of a ground squirrel infestation (Munch et al., 1933). Recently, thallium has been utilized in the manufacturing of optical lenses, semiconductors, scintillation counters, low temperature thermometers, green-colored fire works, imitation jewelry, and chemical catalysts. The therapeutic use of these salts has been abandoned, but the hazards of an accidental ingestion of

thallium-containing rodenticides, or its use in homicidal or suicidal ingestion, occur occasionally (Bank et al., 1972; Cavanagh et al., 1974; Mathews and Anzarut, 1968; Moore et al., 1993; Papp et al., 1969; Reed et al., 1963; Smith and Doherty, 1964).

The clinical manifestations of acute thallium poisoning, consisting of the characteristic dermatological findings of alopecia, hyperkeratosis, and Mees' lines in nails, have been well described (Galvan-Arzate and Santamaria, 1998; Prick, 1979; Tromme et al., 1998). The neurological symptoms include dysesthesia, painful neuropathy, muscle weakness, cranial nerve palsies, ataxia, tremor, convulsion, coma, and death (Dumitru and Kalantri, 1990; Prick, 1979; Van Kesteren, 1994; Yokoyama et al., 1990). The term "encephalopathia thallica" implies a variety of conditions, from non-specific giddiness, lack of drive, and memory impairment, to a decline in intelligence and irreversible dementia (Prick, 1979). Neuropathological studies of the brain are limited and reveal edematous changes and vascular engorgement in the cerebral hemispheres, and chromatolytic changes in the motor cortex, globus pallidus, substantia nigra, and brainstem nuclei (Davis

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et al., 1981; Kennedy and Cavanagh, 1976; Prick, 1979; Tanaka et al., 1978). Neuroimaging studies of the brain are likewise rare (Insley et al., 1986). Recently, we encountered two patients with thallium intoxication who developed confusion in the acute stage, followed by cognitive impairment. Herein, we report the central nervous system (CNS) manifestations, neuropsychological studies, and brain magnetic resonance image (MRI) findings of acute thallium intoxication.

2. Case report

2.1. Patient 1

On March 15, 2002, a 48-year-old woman developed nausea, vomiting, loss of taste, and perioral numbness a few hours after drinking approximately 750 mL of bottled water and eating breakfast. Generalized myalgia was experienced in the afternoon, and progressed to severe painful dysesthesia in the soles of the feet on the following day.

On examination, she had excruciating bilateral leg and foot pain that was aggravated from touching the lower extremities. She could not tolerate extensive neurological examinations due to severe allodynia. Her vital signs were normal, and her family and past histories were unremarkable. She was confused and disoriented to time, place, and person; she had incoherent speech, lacked attention, delusion, and reported visual hallucinations. Deep tendon hyper-reflexia was observed in all upper and lower extremities while plantar reflexes were normal. Dry mouth, decreased salivation, and aphthous ulcers were also noted.

Laboratory examinations showed normal hemograms, serum glucose, renal function, and electrolytes, with aspartate aminotransferase (AST): 21 U/L, alkaline phosphatase: 38 U/L, and a slightly increased level of alanine aminotransferase (ALT): 85 U/L (ref.: 0–36 U/L). The initial electroencephalography (EEG) showed diffuse theta waves indicating a mild diffuse cortical dysfunction. Brainstem auditory evoked potentials (BAEP) and visual evoked potentials (VEP) studies were normal.

One week later, erythematous skin rashes appeared on the face, cheek, and perioral areas, and they became acneiform or pustular eruptions. Visual hallucination, confusion, and disorientation to time, place, and person were still present. In addition, there was a multi-directional gazing nystagmus. The secretion of both saliva and tears was reduced. She also had diarrhea, and tachycardia (100–130 beats/min). Urine retention was noted, and her urodynamic examinations revealed detrusor hyporeflexia and a low urinary flow rate. Initial brain MRI images were performed on April 3, 2002, which showed hypointense lesions in T1 weighted images (T1WI), hyperintense lesions in T2 weighted images (T2WI), and fluid-attenuated inversion recovery in the corpus striatum (Fig. 1). Three weeks later, a loss of scalp hair started.

2.2. Therapy

The patient was treated with intravenous infusion for forced diuresis since intoxication was suspected to have occurred.

Activated charcoal was also started and Prussian blue 1 g daily in four divided dosages was available until 3 weeks later while a definite diagnosis was made from the toxic level of urinary thallium. The hair loss continued for 1 month until a nearly total loss of scalp hair occurred. Hair loss was also noted in the lateral aspect of the eyebrows, but the eyelash, axillary hair, and pubic hair were relatively preserved. At the same time, muscle weakness and hyporeflexia of the lower limbs developed. One month after intoxication, scaling on the soles of her feet was found and persisted for 1 month. In addition, a prolonged (10 h) hemoperfusion was performed twice to more rapidly enhance thallium elimination. Prussian blue 1 g every 8 h was continued until June 10, when urinary thallium elimination decreased to 65.6 $\mu\text{g}/\text{day}$. The repeated brain MRI on April 30 showed that the lesions had resolved. Two months later, the follow-up EEG was also normal. The Mees' lines appeared 3 months later. The Mini-Mental State Examination (MMSE) was performed 2 months later, and yielded 17 (total score 30) in this patient. Neuropsychological studies performed by a Chinese version of the neuropsychological test battery which has been commonly used in the Taiwanese population (Kuo et al., 2005a; Lin et al., 2003) and also showed impairments in digital span (backward), memory registration, memory recall, memory recognition, verbal fluency, judgment of line orientation, and proverb reasoning. However, the comprehension, repetition, naming of language, construction, and calculation were normal. Six months later, the MMSE showed an improvement with a score of 28 in this patient. In addition, her neuropsychological status improved but memory registration, memory recall, memory recognition, and verbal fluency remained abnormal. However, agitation, aggression, anxiety, a depression, sleep disturbance, and emotional lability were found by a test of the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994). The patient was treated each day with gabapentin 1600 mg and amitriptyline 75 mg daily for relief of neuralgia during the 1-year follow-up period.

2.3. Toxicology survey

The heavy metal survey of the urine, using inductively coupled plasma mass spectrometry (ICPMS) (Perkin-Elmer SCIEX ELAN model 5000), showed a high concentration of thallium, with 14,520 $\mu\text{g}/\text{L}$ (ref.: 0–10 $\mu\text{g}/\text{L}$) on March 20, while the levels of mercury, lead, cadmium, arsenic, manganese, nickel, zinc, copper, bismuth, tellurium, and stibium were unremarkable. The blood thallium level was 2056 $\mu\text{g}/\text{L}$ on March 20.

In the food samples, there was neither thallium or arsenic, nor other toxic heavy metals. However, in the bottled water, a very high concentration of thallium (3124 mg/L) was noted. The thallium concentrations of water from other places such as tap water, and drinking water from the same building were normal. Serial 24-h urinary concentrations of thallium gradually decreased from 1177.9 $\mu\text{g}/\text{day}$ on May 3, to 65.6 $\mu\text{g}/\text{day}$ on June 10. The blood thallium levels were also decreased from 455 ng/g on April 16, to 4.7 ng/g on June 20.

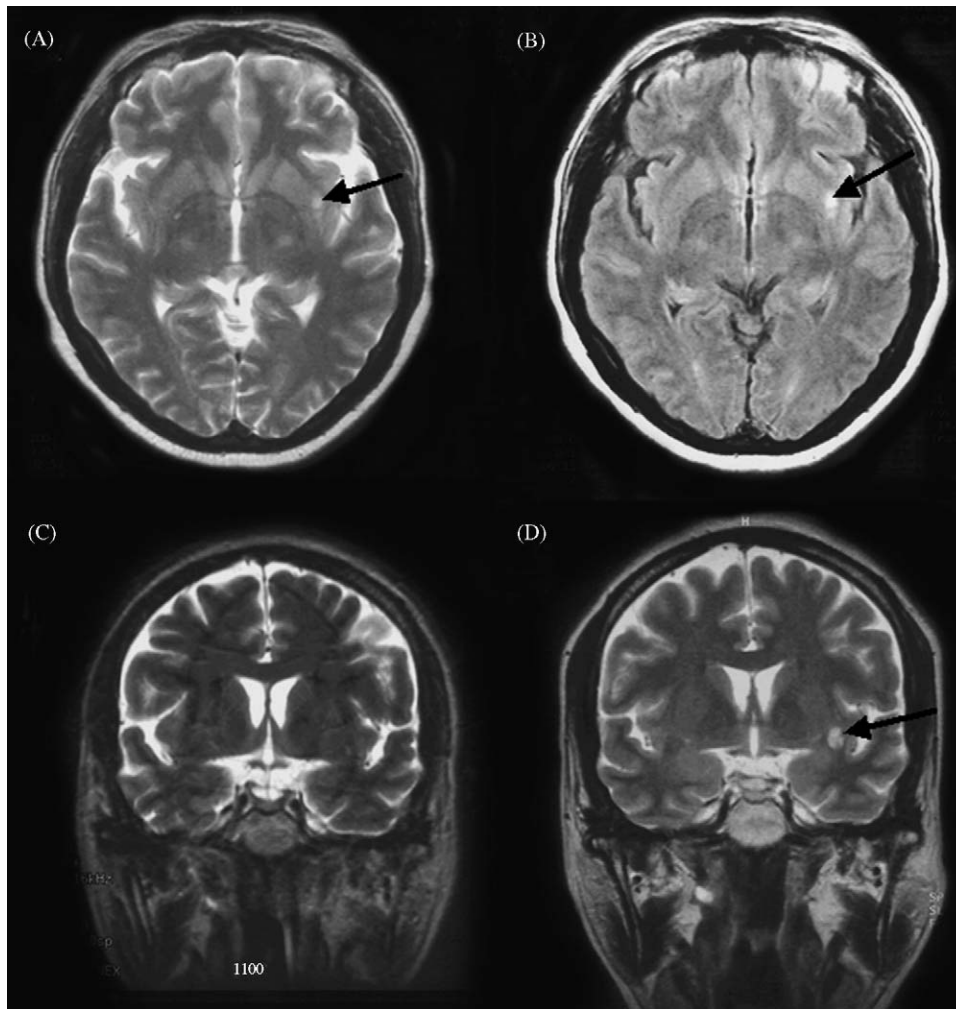


Fig. 1. Initial brain MRI showing increased signal intensity lesions (arrows) in the corpus striatum on T2W (A) and FLAIR (B), 2 weeks after thallium intoxication and a follow-up brain MRI 6 weeks later showing that the lesions had resolved (C) as compared with the previous lesions (D).

2.4. Patient 2

A 52-year-old man (husband of patient 1) developed an acute onset of perioral numbness, a decrease of taste sensation, nausea, and poor appetite a few hours after drinking of the same bottled water (about 500 mL) and finishing his breakfast on March 15, 2002. Aching pain in both distal lower limbs was experienced at night. On the following day, paresthesia and dysesthesia were noted in the distal lower extremities. During the examination, the vital signs were stationary and his consciousness was clear except for disorientation to time and lack of attention. In addition, dry mouth and generalized hyperreflexia were found. Biochemistries revealed an increased total bilirubin level: 1.8 mg/dL (ref.: 0.0–1.3 mg/dL), ALT: 80 U/L (ref.: 0–36 U/L), but normal renal, and thyroid functions. The EEG, BEAP, and VEP were normal. Erythematous skin rashes appeared on the face, cheek, and perioral regions 1 week later. In the second week, the skin rashes transformed to acneiform or pustular eruptions. Alopecia started in the third week, particularly the scalp hair, and lateral aspect of the eyebrows. Furthermore, tachycardia, urinary retention, and diarrhea were

also observed. Bilateral distal leg muscle weakness developed in the second week along with scaling of the soles of the feet. The initial brain MRI studies on April 3 were normal. The score of MMSE was 19. Neuropsychological tests revealed impairments in digital span (backward), memory registration, memory recall, memory recognition, verbal fluency, and similarity. The Mees' lines were noted at the end of the second month. However, 6 months later, the MMSE score was improved to 29. In addition, the neuropsychological studies also improved except verbal fluency. In the 1-year follow-up period, he still had anxiety, depression, memory impairment, and emotional lability.

2.5. Therapy

In the acute stage, he was treated with an intravenous infusion of normal saline for forced diuresis and activated charcoal. In addition, gabapentin and amitriptylline were also given for relief of painful extremities. After a definite diagnosis 3 weeks later, a therapy of Prussian blue 250 mg every 6 h was available and started. The Prussian blue was increased to 1 g

every 8 h and continued in the following 2 months after the daily urinary concentration was decreased to 38.7 $\mu\text{g}/\text{day}$ on June 10. In addition, two courses of prolonged hemoperfusion were also performed.

2.6. Toxicology survey

The heavy metal survey of the urine revealed 11,326 $\mu\text{g}/\text{L}$ of thallium and the blood thallium level was 950 $\mu\text{g}/\text{L}$ on March 20. Serial 24-h urinary concentrations of thallium gradually decreased from 977.4 $\mu\text{g}/\text{day}$ on May 3, to 38.7 $\mu\text{g}/\text{day}$ on June 10. The blood thallium levels were also decreased from 306 ng/g on April 16, to 1.9 ng/g on June 20.

3. Discussion

We present the sequential changes in the clinical features and neurological manifestations of two patients with acute thallium intoxication. The prominent CNS symptoms were confusion, incoherent speech, delusion, and visual hallucination in the acute stage, and anxiety, depressive mood, lack of attention, memory impairment, and emotional lability in the chronic stage. Initial neuropsychological test revealed impairments in digital span, memory registration, memory recall and memory recognition, reasoning for similarity, proverb reasoning, and verbal fluency 2 months later. The follow-up neuropsychological test 6 months later showed a prominent improvement except memory registration, memory recall, and memory recognition in patient 1 and verbal fluency in both patients.

The couple developed severe pain in both feet, erythematous skin rashes, peripheral neuropathy and alopecia. The clinical manifestations strongly indicated arsenic or thallium intoxication. The heavy metal survey with ICPMS 2 weeks later confirmed thallium poisoning from the bottled water, which eventually proved to be deliberately tainted. In the peripheral nervous system, a primarily distal axonopathy involving both large and small myelinated fibers and even unmyelinated fibers, particularly in the lower extremities, has been reported elsewhere compatible with the previous studies (Dumitru and Kalantri, 1990; Kennedy and Cavanagh, 1976; Kuo et al., 2005b; Yokoyama et al., 1990).

Thallium intoxication may induce CNS and peripheral pathology (Prick, 1979; Van Kesteren, 1994). Prominent effects include central neuropathies, ataxia, tremor, and mental disturbances (Munch et al., 1933). Mental disturbances include poor attention, anxiety, depression, altered consciousness, hallucination, and paranoid syndromes (Prick, 1979; Tanaka et al., 1978; Van Kesteren, 1994). Interestingly, our patients developed hyper-reflexia initially, and 2 weeks later, the tendon reflexes changed to hypo-reflexia. The data indicated that the upper motor neuron lesions might have been present since the acute stage. Initially, patient 1 had incoherent speech, confusion, delusion, and hallucination, correlated with diffuse slow waves on the EEG, as compared with patient 2. Patient 1 also ingested a relatively higher amount of thallium (about 2.4 g) than patient 2 (about 1.5 g).

In addition, urinalysis confirmed a higher urine thallium concentration in patient 1 as compared with that of patient 2 (14.5 mg/L versus 11.3 mg/L). The data indicated that a higher thallium exposure might induce a more prominent CNS symptomatology.

Both patients had mental impairments with neurotic-like symptoms and a depressive mood in the 1-year follow-up period. Serial neuropsychological tests also confirmed a disturbance including reversed digital span, memory registration, memory recall, memory recognition, and verbal fluency. The data indicated a selective involvement of the temporal lobe and its related structures. In previous reports, mental disturbances and symptomatic epilepsy may present, particularly in patients with lesions in the temporal lobes (Prick, 1979). To our knowledge, neuroimaging studies have rarely been done (Insley et al., 1986). Normal brain CT or MRI scans have been reported in patients with cognitive impairments and frequent aggressive outbursts after thallium poisoning (Insley et al., 1986; McMillan et al., 1997). Initial brain MRI studies of patient 1 also revealed lesions in the corpus striatum. This lesion was no longer noted in the follow-up MRI. From the above data, the neuropsychological findings were not compatible with the brain MRI abnormalities. However, the neuropsychological impairments persisted longer than the lesions in the brain MRI. The brain MRI lesions presented only in one patient. Although it is difficult to make a definitive conclusion, brain MRI studies may reveal acute effects due to severe thallium poisoning. In addition, although the underlying pathology is unknown, previous pathological studies have shown alterations in the cortical and corpus striatum neurons, with central chromatolysis, and edematous changes in the subcortical white matter (Kennedy and Cavanagh, 1976; Prick, 1979; Tanaka et al., 1978). In our patient 1, the hypointense lesion in T1-weighted images and the hyperintense lesion in T2-weighted images might indicate an edematous change or demyelination.

The cellular mechanisms of thallium toxicity include the substitution of potassium in Na–K-ATPase, as well as a high affinity for the sulfhydryl or thiol group of mitochondrial membranes (Prick, 1979). Therefore, thallium inhibits many enzyme reactions and protein production. However, the mechanisms of differential involvement in the corpus striatum and asymmetrical lesions in brain MRI were unclear. In human and experimental studies, the highest thallium concentrations were found in the corpus striatum, thalamus, and hypothalamus (Davis et al., 1981; Insley et al., 1986). It was also noted that thallium accumulated more rapidly in the hypothalamus and corpus striatum than in other brain regions (Brown et al., 1985; Rios et al., 1989). However, further investigations on the pathogenesis of differential and asymmetrical involvements are warranted.

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