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Mini-Review

Acute thallium intoxication: An experience in Taiwan

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ABSTRACT

Although acute thallium intoxication may induce various clinical features, it mainly results in dermatological and neurological deficits. Skin changes include a peculiar deposit of a dark pigment in the hair roots several days after intoxication, followed by hair loss 10 days later and complete alopecia 3 to 4 weeks later. In addition, the impairment of sweat and sebaceous glands and hyperkeratosis are also noted. Typical Mees' lines appear in the fingernails and toenails 2-3 months later. Dermatological deficits may subside 3 months later. The neurological deficits of acute thallium intoxication include severe painful neuropathy and a debilitating encephalopathy. The neuropathy is usually painful, and excruciating pain is the most prominent symptom. It usually appears in the following day after acute thallium intoxication and may persist for a long time. Axonal damage may involve both the large and small fibers. Free nerve endings of the skin are severely damaged and the recovery is partial. The central nervous system (CNS) is also severely involved. The term "encephalopathia thallica" encompasses a range of CNS damages, including memory deficits and cognitive impairment. Brain magnetic resonance images show lesions in the corpus striatum. Functional neuroimage such as by fluorodeoxyglucose positron emission tomography also shows a decreased uptake in the cingulate gyrus and diffuse cortical area. No specific antidote is available for thallium intoxication. However, gastric lavage, activated charcoal, hemoperfusion and Prussian blue may be helpful to prevent further damages.

KEYWORDS: thallium poisoning, alopecia, neuropathic pain, Mees' line, encephalopathy, functional neuroimages, MRI, FDG-PET, therapy

INTRODUCTION

Thallium (Tl), which has an atomic weight of 204.37, classified in the group III A of the periodic table, is a trace element in the earth. It was discovered spectroscopically first in May 1861 by William Crookes [1-4]. The element name is derived from the Greek word "thallos" indicating a green shoot or twig. Thallium is a soft, malleable, lustrous, silver metal with a low melting point. It resembles lead in appearance and can easily be cut with a knife. Pure thallium exists in the nature and is widely distributed in the form of various minerals and ores. The metal is recovered as a by-product during sulfuric acid production. Thallium can also be obtained from the smelting of lead and zinc ores. In the 19th century, thallium acetate (CH3COOTl) was used in treating refractory diarrhea, syphilis and nocturnal sweating. Thallium sulfate (Tl_2SO_4) had also been widely employed in rodenticides and insecticides since 1920 because it is odorless, colorless, and tasteless. However, its toxic effects include baldness, loss of axillary and public hairs, nausea, vomiting, diarrhea, allodynia, and distal muscle weakness, particularly in the lower extremities [1-3]. Thus, the use of some pesticides containing thallium was prohibited in

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some countries because of the potential dangers of thallium's residual toxicity. Thallium poisoning is rarely seen nowadays, except in some cases of accidental ingestion, suicide or crime events [1-4]. Thallium is still used in the semiconductor industry (thallium sulfate), low- range thermometers, optical systems and photoelectric cells (thallium sulfate), signals at sea (thallium nitrate), highly refractive glass, artificial gems (thallium oxide), low-melting glass, photocells, fireworks (thallium nitrate), and as a catalyst in chlorination (thallium chloride). Medically, thallium has also been used in the detection of acute myocardial injury (thallium isotope 201, ^{201}Tl) and as a pesticide for controlling of rodents and insects in some geographic areas. Thallium has 2 stable isotopes ^{203}Tl and ^{205}Tl. In the earth, ^{205}Tl is the most common isotope with an abundance of 70.5% [1-5]. This mini-review is based on the experience of acute thallium intoxication that occurred in Taiwan [6-9]. Since 2002, two patients developed acute confusion, severe painful neuropathy, and skin lesions after attempted homicide by ingestion of thallium contaminated water. A long-term follow-up study was conducted in the following 10 years.

Kinetics of acute thallium intoxication

Thallium is absorbed easily through the digestive tract, respiratory tract, and skin. Most reported studies document oral exposure with few reports of toxicity caused by inhalation exposure or dermal exposure. The peak plasma concentration can be noted 2 h after oral administration. Thallium salts are slowly distributed through the body and excretion of thallium through feces and urine takes more than 90 days [1-5]. Determination of thallium levels in various tissues is also important in the distribution and diagnosis of thallium intoxication [6-10]. Sequential thallium concentrations of various tissues have been reported in 2 patients who drank water that contained high concentrations of thallium (patient 1: 2056 ug/L, patient 2: 956 ug/L) [11-14]. Patient 1 had a lower initial urinary thallium level (patient 1: 11400 ug/L, patient 2: 11900 ug/L). Both blood and urinary thallium levels decreased rapidly in the first month. One month later, patient 1 had 15% and 40% of the initial thallium level in the blood and urine respectively, and patient 2 had 25% and 22% in the blood and urine, respectively. Two months later, the thallium concentrations had greatly decelerated (Patient 1: 0.36% in blood and 0.32% in urine, patient 2: 1.63% in blood and 0.85% in urine). About 3 months later, the blood thallium concentrations returned to nearly normal but are still detectable in both patients (patient 1: 4.7 ug/L in; patient 2: 1.9 ug/L). Thallium was also found in the fingernails samples of the patients (patient 1: 3.9 ug/g on the 38th day, and patient 2: 4.4 on the 35th day, respectively). Thallium concentrations in the hair samples also decreased mainly in the first 2 months after intoxication. However, the thallium levels in the stool samples reached a plateau around the 40th day. Subsequently, thallium levels decreased rapidly until the 50th day after intoxication. A slow decrease was noted thereafter with minimal detection of thallium level noted on the 89th day (patient 1: 0.35 ug/g; patient 2: 0.37 ug/g). Figure 1 shows the serial changes in the blood, urine, hair and stool samples in 1 patient with acute thallium intoxication.

Cellular mechanisms of thallium toxicity

Several cellular mechanisms of thallium toxicity have been reported previously. First, the substitution of potassium in Na-K-ATPase allows easy transport of thallium through the membrane to the cytoplasm, leading to the failure of maintenance of a high K+ concentration in the intracellular area. Second, thallium has a high affinity for the sulfhydryl or thiol group of mitochondrial membranes and then thallium can inhibit many enzymatic reactions and protein production. Furthermore the keratin formation is inhibited, leading to disruption of hair growth and alopecia as well as the development of Mees' line. In addition, thallium has an effect on the formation of complex protein molecules. Another effect of thallium poisoning is the disruption of heme metabolism, as indicated by the presence of porphyrins in the urine. The presence of thallium in the neurons can alter carbohydrate metabolism and subsequently impair the energy production in the nervous tissues [1-3].

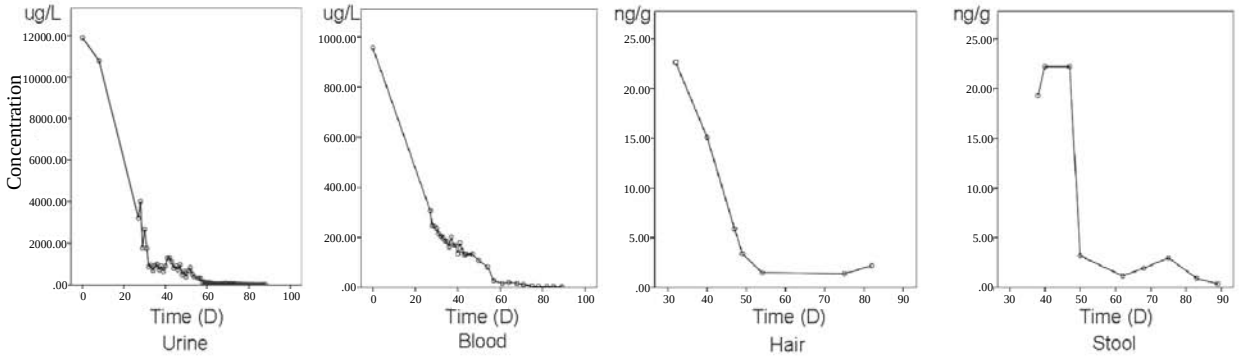

Figure 1. Represents serial concentrations of thallium in the blood, urine, hair and stool samples in a patient with acute thallium concentration. The thallium level decreases in the first month rapidly and returns to a nearly normal level 3 months later.

Clinical manifestations

Gastrointestinal tract symptoms

After ingestion of the thallium salts, nausea, vomiting, and taste changes are noted within minutes. Usually abdominal pain particularly in the epigastric areas and gastritis with hemorrhages follow. In the acute stage, dry mouth and diarrhea persist for several days or weeks. Later on, severe constipation due to paralytic ileus is experienced for several weeks [15-18].

Cutaneous manifestations

The dermatological features have been reported in acute, subacute, and chronic thallium intoxication [13, 19-25].

During the acute stage, dry mouth and loss of taste develops within hours. Several days later, erythematous skin rashes appear on the face usually on the cheeks and perioral areas. By the following week, the skin lesion transforms to acneiform or pustular eruptions. Loss of hair develops in the scalp area around 2-3 weeks later, followed by loss of lateral portion of the eyebrows. Hair loss is not as prominent in the eyelash and pubic areas. Hyperkeratosis is observed in the fingers approximately 1 month later. Usually hair can be easily pulled out without pain, and complete alopecia develops 3-4 weeks later (Figure 2). Hair re-growth and follicular plugging generally appear after 2-3 months. Mees' lines develop in the fingernail and toenails 1-2 months later. However alopecia is not always present and is not specific to thallium poisoning. Alopecia can also accompany arsenic poisoning and is dependent on the amount and/or duration of thallium intoxication. Skin biopsy specimens taken from the facial lesions show marked parakeratosis, mild epidermal atrophy and vacuolar degeneration of the basal layers. In addition, dilated hair follicles are filled with keratin and necrotic sebaceous materials. Perivascular and periadnexal infiltrates of mononuclear cells are also noted [13] (Figure 3).

Central nervous system manifestations

The term "encephalopathia thallica" encompasses a range of conditions from non-specific giddiness, lack of drive, memory impairment, confusion, incoherent speech, tremors, choreoathetoid movement, convulsion, ataxia, and coma [1, 2, 26-29]. Mental disturbances include anxiety, neurosis, insomnia, paranoid, mental confusion, delusion, hallucination, psychosis, and irreversible dementia. The accompanying electroencephalography (EEG) usually shows diffuse theta waves indicating a diffuse cortical dysfunction in severe intoxicated patients. Brain magnetic resonance images (MRI) show increased signal lesions in the corpus striatum [11] (Figure 4). Pathological changes reveal alterations in the cortical and corpus striatum neurons, with central chromatolysis and edematous changes in the subcortical white matter [29-31].

Neuropsychological studies

Neuropsychological tests have been carried out in thallium poisoning [11, 32, 33].

Neuropsychological studies show impairment in digital span, memory, recognition, verbal fluency,

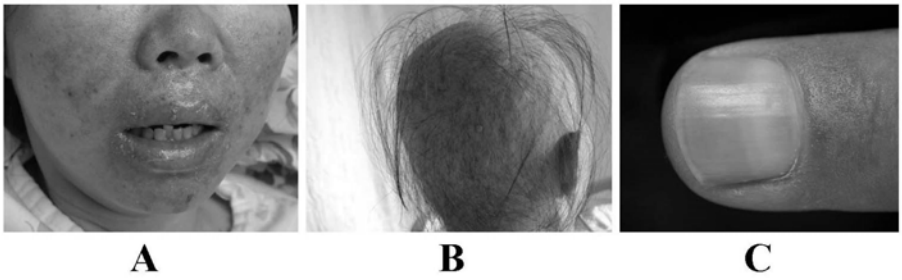

Figure 2. A) Erythematous skin lesions with acneiform or pustular eruption appear in the perioral area 1 week later, B) Loss of scalp hair to nearly alopecia l-2 months later, C) Mees' lines appear in the fingernail 3 months after acute thallium intoxication.

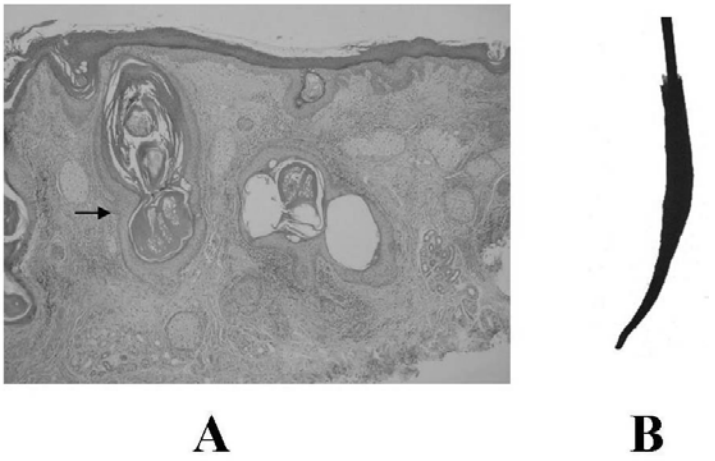

Figure 3. A) Skin biopsy showing dilated hair follicles with keratin and perivascular and periadnexal mononuclear cell infiltrations in microscopic examination (Hematoxylin-Eosin stain X40). B) Microscopic examination of the hair samples showing abnormal anagen hair with a tapered dystrophic root and a hard loose sheath.

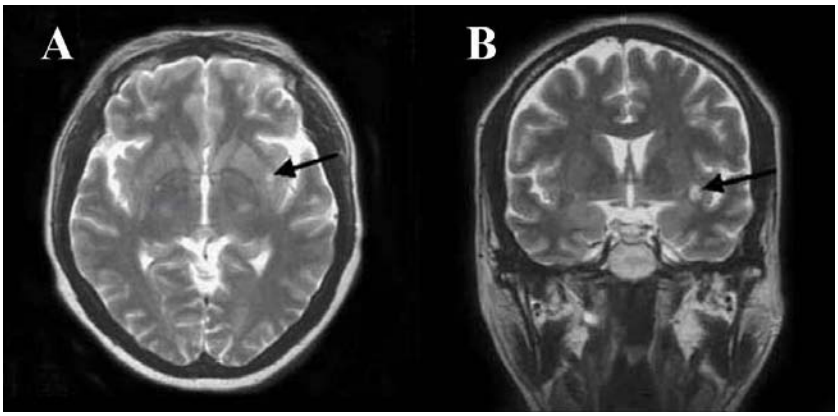

Figure 4. Brain magnetic resonance imaging (MRI) showing a high signal intensity lesion in the corpus striatum on T_2W (A) (horizontal view) and FLAIR (B) (coronal view).

judgment in line orientation, and proverb reasoning. In addition, agitation, aggression, depression, sleep disturbance and emotional lability are found in the Neuropsychological Inventory [11]. A longitudinal study of serial cognitive alteration with neuropsychological studies conducted in 2 patients with acute thallium intoxication revealed abnormalities in Mini-Mental Status Examination (MMSE), reversed digital span, similarity proverb reasoning, memory registration, memory recall, memory recognition and trial making test. Both patients had a particular disability in self-caring (Patient 1: 11/17; patient 2: 5/17) by the Blessed Dementia Rating Scale. During long-term follow-up, the clinical recoveries of initially impaired cognitive dysfunction mainly occurred in the first 6 months. However even 10 years later, the cognitive function was not fully recovered [14].

Brain positron emission tomography (PET) scan

18-Fluorodeoxylglucose positron emission tomography (^{18}FDG PET) scan of the brain was performed in 2 patients after thallium intoxication [14]. The PET studies revealed a decreased uptake of glucose in the cingulate gyrus, both frontal lobes, and parietal lobes in both patients. One patient also received a second brain PET scan 2 months later and this showed a partial recovery of the previous abnormality.

Peripheral nervous system manifestation

Peripheral neuropathy associated with neuropathic pain has been reported after acute thallium intoxication [1-5, 12, 34-38].

The peripheral neuropathy associated with thallium intoxication is a distal, symmetric axonopathy that preferentially affects large diameter fibers. The symptoms are mainly sensory complaints much more than motor weakness and severe pain is a prominent feature. Acute thallium intoxication may induce damages to the peripheral nervous system including paresthesia, dysesthesia, and allodynia. In the sensory function, hyperesthesia and allodynia are noted during the acute stage. Two weeks later, hypoesthesia to pin-pricks and temperature sensation develop. In the motor function, tendon reflexes are normal in the hyperacute stage followed by the development of hyporeflexia 2 weeks later and areflexia within 1 month. Muscle strength rapidly deteriorates within 1 month and remains a plateau for 2 months. Three months later, a slight improvement is observed in pin-pricks and pressure sensation but cold and warm sensations do not improve. All sensory modalities show a partial improvement after 6 months [12].

With a moderate degree of thallium ingestion, a subacute variety is seen. Subacute thallium neuropathy evolves more slowly, beginning more than 1 week after exposure [18]. The neuropathy is characterized by sensory greater than motor deficit. All modalities are affected (proprioception, light touch, and pin-pricks). Walking may be affected early on, mainly due to painful paresthesia in the feet. Although some degree of distal weakness is detected, it is rarely severe. The deep tendon reflexes are slightly reduced or normal in the subacute phase. The chronic form of thallium neuropathy is occasionally seen. This neuropathy results from a prolonged low-level exposure to moderate levels of thallium.

Nerve conduction studies and quantitative sensory testing

Electrophysiological studies have been conducted in patients with thallium poisoning [12, 39, 40]. Nerve conduction studies (NCS) reveal a decreased amplitude of compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs) but a slight slowing in distal latencies (DLs) and motor and sensory nerve conduction velocities (MNCV and SNCV) in the median, ulnar, deep peroneal, tibial and sural nerves involving both motor and sensory fibers [12]. The involvement is more prominent in the lower extremities. The data indicate a dying-back axonal polyneuropathy. Quantitative sensory testing also reveals impairment in pinprick, temperature, touch, vibration and position sensations. Serial NCS data in 2 patients showed minimal improvement 10 months after intoxication. Over a 9-year follow up, 1 patient showed a prominent improvement of motor NCS in the deep peroneal and tibial nerves including DL, amplitude (A), and nerve conduction velocity (NCV). However, a limited recovery of sensory NCS especially in the sural nerve was noted in the lower limbs. The other patient with initially absent CMAP of deep peroneal nerves

only showed minimal improvement in the deep peroneal and sural nerves, but had gradual recovery in the tibial nerve (Figure 5).

Pathological studies in sural nerve and cutaneous nerve biopsies

Previous nerve biopsies have shown axonal degeneration with a preservation of the overlying myelin or secondary myelin degeneration [29, 30]. In patients with acute thallium intoxication, sural nerve biopsy studies show many degenerated axonal fibers with disrupted myelin sheaths. On electron-microscopic examination, a loss of normal arrangement of the neurofilaments, fragmentation, and separation of the myelin lamellae with atrophic axon are noted. Histogram of the myelinated nerve fibers from the sural nerve biopsy demonstrates a decrease in the number of large myelinated fibers [12] (Figure 6). Cutaneous nerve biopsy studies using protein gene product 9.5 confirm a loss of epidermal nerves indicating an involvement of the small sensory fibers. A follow-up cutaneous nerve biopsy 1 year later still reveals only a beard-like appearance of the free nerve ending [12, 13] (Figure 7).

Autonomic manifestations

Damages to the autonomic nervous system including irregular heart beats, cardiac arrhythmia, hypertension/hypotension, and angina-like pain, leading to heart failure have been reported [41]. The neuropathy of the parasympathetic nervous system is responsible for the cardiac and circulatory dysfunction. In addition, urine retention and sexual impotence were also commonly noted in acute thallium intoxicated patients. A delayed autonomic

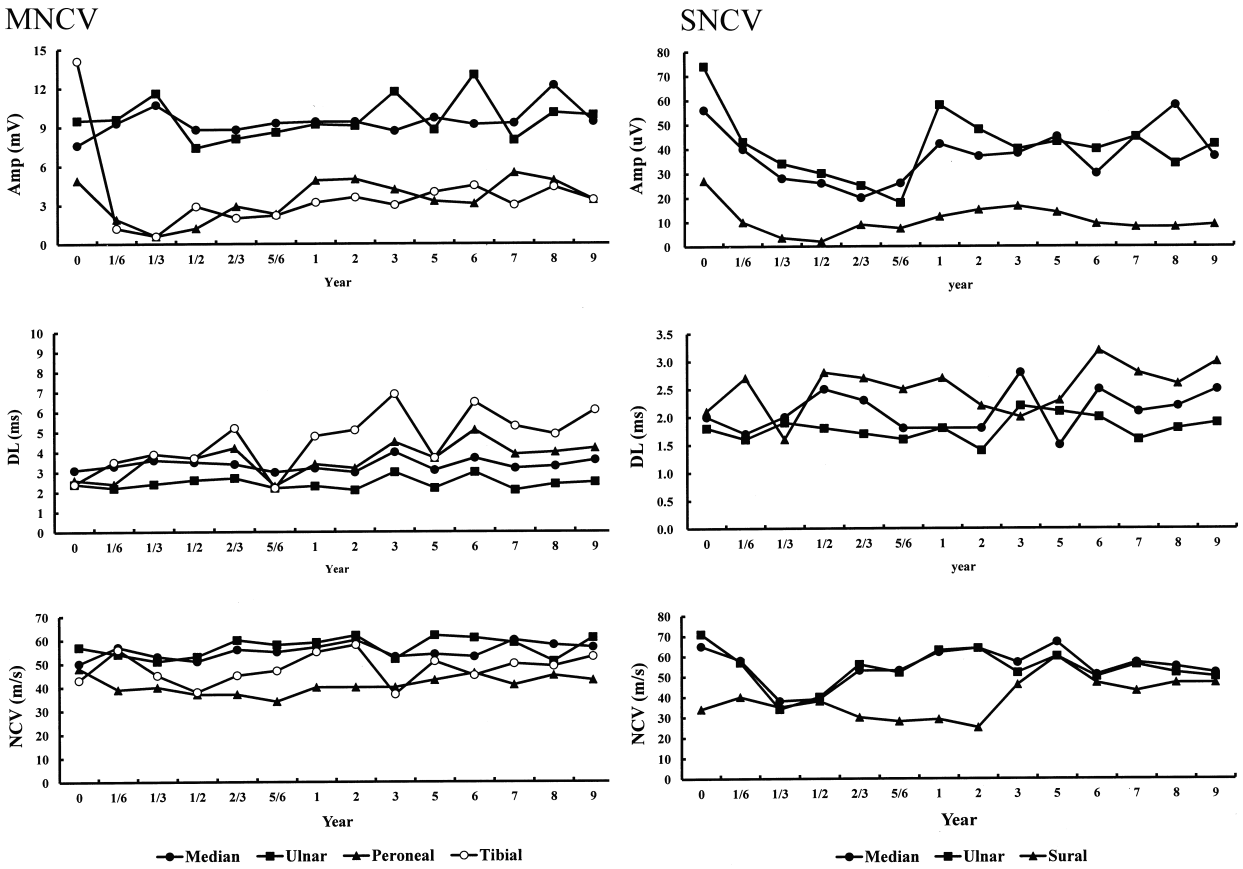

Figure 5. The 10 years long-term follow-up studies of serial nerve conduction velocity in a patient with acute thallium intoxication. (M: median nerve, V: ulnar nerve, P: peroneal nerve, T: tibial nerve, S: sural nerve, DL: distal latencies, Amp.: amplitude, NCV: nerve conduction velocity).

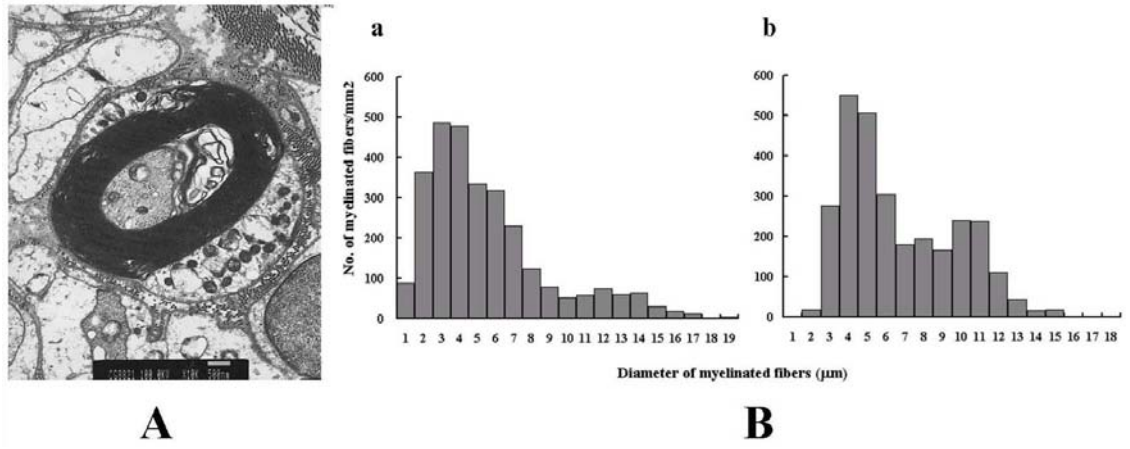

Figure 6. A) Electron microscopic examination in the sural nerve biopsy showing an abnormal axon with degenerated myelin. B) Histogram of fiber diameters in the myelinated nerve fibers showing a decrease of large myelinated fibers (a) in a patient with acute thallium intoxication and compared with a normal control (b).

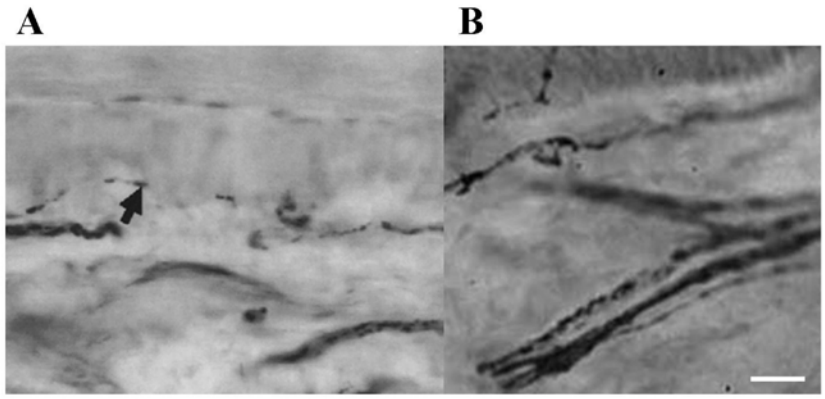

Figure 7. Cutaneous nerve biopsy stained with protein gene product 9.5 (PGP 9.5) showing a fragmented dermal nerve fiber in the subepidermal area in a patient with acute thallium intoxication (A) as compared with a normal control (B) bar : 1 µm.

neuropathy due to the involvement of small unmyelinated fibers may also appear after acute intoxication.

Cardiac manifestation

Extensive damage to the myocardium with myofibril thinning, myocardial necrosis and inflammation and accumulation of lipid droplets has been reported in human studies. Sinus bradycardia, ventricular arrhythmias and T-wave anomalies are noted. In animal studies, heart block, atrial and ventricular ectopic arrhythmia with T-wave fluttering, prolonged Q-T interval, and ST segment depression or elevation were observed after thallium intoxication [12]. Cardiac and pulmonary manifestations are reported to be the primary non-neurogenic problems associated with thallium intoxication especially in the acute stages of this illness [42].

Renal manifestation

Renal function is usually not grossly impaired. However severe thallium intoxication may affect the kidney causing extensive necrosis of the renal cortex because of infarction. Renal function is impaired with hematuria, diminished creatinine clearance, and elevated blood urea nitrogen and albuminuria [1, 4, 5, 43].

Ophthalmological manifestations

Ophthalmological changes from thallium intoxication include lens opacity, retrobulbar neuritis, optic neuropathy, and ophthalmoplegia [44]. The early changes before optic atrophy include diminished contrast sensitivity, a tritan defect in color vision (blue-green color defect) and related cecocentral scotoma, as well as occasional internal and external ophthalmoplegia and nystagmus [45, 46]. Animal studies show that the retina especially the photoreceptor layer is susceptible to thallium toxicity. Iritis, intraocular hemorrhage, and eyelid inflammation have also been reported [47].

Treatment

There are no specific antidotes for thallium poisoning. Therapeutic principles include (1) elimination of thallium that is not yet absorbed by the digestive system such as through gastric lavage with a nasogastric tube in the early stage of poisoning particularly within 4 h of oral administration; (2) administration of laxatives and activated charcoal to increase thallium excretion in stool; (3) increased renal secretion with fluid intake and forced diuresis; (4) hemoperfusion instead of hemodialysis, particularly in severe thallium poisoning; (5) Prussian blue administration to increase the urinary and fecal excretion of thallium [1-4, 48]. In recent years, Prussian blue therapy has been proven the most effective treatment for acute thallium poisoning [49-53]. In addition, administration of potassium has a positive effect on urinary thallium excretion in rats [54]. However, caution is required because potassium may mobilize thallium more quickly than it can be eliminated [2, 43]. It is also very important to relieve the painful neuropathy by using drugs such as antidepressants e.g. tricyclic antidepressants; antiepileptics, eg. carbamazepine, gabapentin, and diphenylhydantoin; and serotonin/ norepinephrine reuptake inhibitor (SNRI) e.g. duloxetine. Most patients also require long-term psychotherapy, physical therapy and occupational therapy to overcome other adverse effects during the recovery period.

ABBREVIATION

CNS : central nervous system
EEG : electroencephalography
MRI : magnetic resonance images
NPI : neuropsychological inventory
MMSE : mini-mental status examination
BDRS : blessed dementia rating scale
PET : positron emission tomography
^{18}FDG : [^{18}F]-deoxyglucose
CMAP : compound muscle action potential
SNAP : sensory nerve action potentials
MNCV : motor nerve conduction velocity
SNCV : sensory nerve conduction velocity
NCS : nerve conduction study
DL : distal latency
A : amplitude

REFERENCES

1. Prick, J. J. G. 1979, Handbook of clinical neurology, Vinken, D. J. and Bruyn, G. W. (Eds.), vol. 36, Amsterdam, Elsevier, North-Holland, Biochemical Press, 239.
2. Van Kesteren, R. G. 1994, Handbook of clinical neurology, Vinken, D. J., Bruyn, G. W., and de Wolff, F. A. (Eds.). vol. 64, Amsterdam, North-Holland Pub. Co., 322.
3. Galvan-Arzate, S. and Santamaria, A. 1998, Toxicol. Lett., 99, 1.
4. Carson, B., Ellis, H., and McCann, J. 1986, Chelsea, Mich., Lewis Publishers Inc., 243.
5. Agency for Toxic Substances and Disease Registry U.S. Public Health Service. 1992, ATSDR Toxicological Profiles CRC Press LLC USA.
6. Zhao, G., Ding, M., and Zhang, B., Lv, W., Yin, H., Zhang, L.,Ying, Z., and Zhang, Q. 2008, Eur. Neurol., 60, 292.
7. Pelclova, D., Urban, P., Ridzon, P., Senholdova, Z., Lukas, P., Diblik, P., and Lacina, L. 2009, Hum. Exp. Toxicol., 28, 263.
8. Das, A. K., Chakraborty, R., Cervera, M. L., and de la Guardia, M. 2006, Anal. Bioanal. Chem., 385, 665.
9. Luzanova, I. S., Pletneva, T. V., Maksimova, T. V., Salomatin, E. M., and Lutskii, la. M. 2008, Sud. Med. Ekspert., 51, 41.
10. Sharma, A. N., Nelson, L. S., and Hoffman, R. S. 2004, Am. J. Forensic. Med. Pathol., 25, 156.
11. Tsai, Y. T., Huang, C. C., Kuo, H. C., Wang, H. M., Shen, W. S., Shih, T. S., and Chu, N. S. 2006, NeuroToxicology, 27, 291.

12. Kuo, H. C., Huang, C. C., Tsai, Y. T., Chu, C. C., Hsieh, S. T., and Chu, N. S. 2005, Neurology, 65, 302.
13. Lu, C. I., Huang, C. C., Chang, Y. C., Tsai Y. T., Kuo, H. C., Chuang, Y. H., and Shih, T. S. 2007, Arch. Dermatol., 143, 93.
14. Liu, C. H., Lin, K. J., Wang, H. M., Kuo, H. C., Chuang, W. L., Weng, Y. H., Shih, T. S., and Huang, C. C. Clin Toxicol.
15. Reed, D., Crawleg, J., Faro, S. N., Pieper, S. J., and Kurland, L. T. 1963, J. Am. Med. Assoc., 183, 516.
16. Smith, D. H. and Doherty, R. A. 1964, Pediatrics, 34, 480.
17. Domnitz, C. J. 1960, Southern. Med. J., 53, 590.
18. Loos, H. and Timperman, J. 1959, J. Forensic. Med., 6, 166.
19. Munch, J. C., Ginsberg, H. M., and Nixon, C. E. 1933, JAMA, 100, 1315.
20. Frank, S. B. and Hirsch, D. R. 1952, J. Am. Med. Assoc., 150, 586.
21. Mathews, J. and Anzarut, A. 1968, Can. Med. Assoc. J., 99, 72.
22. Heyl, T. and Barlow, R. J. 1989, Br. J. Dermatol., 121, 787.
23. Moore, D., House, I., and Dixon, A. 1993, Br. Med. J., 306, 1527.
24. Feldman, J. and Levisohn, D. R. 1993, Pediatr. Dermatol., 10, 29.
25. Tromme, I., van Neste, D., Dobbelaere, F., Bouffioux, B., Courtin, C., Dugrnier, T., Pierre, P., and Dupuis, M. 1998, J. Dermatol., 138, 321.
26. Stein, M. D. and Perlstein, M. A. 1959, Am. Med. Assoc. J., 98, 94.
27. Bank, W. J., Pleasure, D. E., Suzuki, K., Nigro, M., and Katz, R. 1972, Arch. Neurol., 26, 456.
28. Cavanagh, J. B., Fuller, N. H., Johnson, H. R. M., and Rudge, P. 1974, Quart. J. Med., 43, 293.
29. Davis, L. E., Standefer, J. C., Kornfeld, M., Abercrombie, D. M., and Butler, C. 1981, Ann. Neurol., 10, 38.
30. Kennedy, P. and Cavanagh, J. B. 1976, J. Neurol. Sci., 29, 295.
31. Tanaka, J., Yonezawa, T., and Ueyama, M. 1978, J. Toxicol. Sci., 3, 325.
32. Thompson, C., Dent, J., and Saxby, P. 1988, Br. J. Psychiatry, 153, 396.
33. McMillan, T. M., Racobson, P. R., and Goss, M. 1997, J. Neurol. Neurosurg. Psychiatry, 63, 247.
34. Insley, B. M., Grufferman, S., and Ayliffe, H. E. 1986, Am. J. Emerg. Med., 4, 545.
35. Moeschlin, S. 1980, Clin. Toxicol., 17, 133.
36. Schaumburg, H. H. and Berger, A. 1992, JAMA, 268, 3430.
37. Downs, W. L., Scott, J. K., Steadman, L. T., and Maynard, E. A. 1960, Am. Ind. Hyg. Assoc. J., 21, 399.
38. Moore, D., House, I., and Dixon, A. 1993, Br. Med. J., 306, 1527.
39. Dumitru, D. and Kalantri, A. 1990, Muscle Nerve, 13, 433.
40. Yokoyama, K., Araki, S., and Abe, H. 1990, Muscle Nerve, 13, 117.
41. Nordentoft, T., Andersen, E. B., and Mogensen, P. H. 1998, NeuroToxicology, 19, 421.
42. Roby, D. S., Fein, A. M., Bennett, R. H., Morgan, L. S., Zatuchni, J., and Lippmann, M. L.1984, Chest, 85, 236.
43. Mulkey, J. P. and Oehme, F. W. 1993, Vet. Human Toxicol., 35, 445.
44. Tabandeh, H., Crowston, J. G., and Thompson, G. M. 1994, Am. J. Ophthalmol., 117, 243
45. Hennekes, R. 1983, Klin. Monbl. Augenheilkd. 182, 334.
46. Shamshinova, A. M., Ivanina, T. A., Yakovlev, A. A., Shabalina, L.P., and Spiridonova, V. S. 1990, J. Hyg. Epidemiol. Microbiol. Immunol., 34, 113.
47. Potts, A. M. 1991, Casarett and Dull's Toxicology, Amdur, M. O., Dull, J., and Klaassen, D. C. (Eds.) 4th Ed., Pergamon, New York, 535.
48. De Groot, G. and van Heyst, A. N. P. 1988, Sci. Total. Environ., 71, 411.
49. Kamerbeek, H. H., Rauws, A. G., Tenham, M., and Vanheijst, A. N. P. 1971, Acta Med. Scand., 189, 149.
50. Rauws, A. G. 1974, Arch. Pharmacol., 284, 295.
51. Thompson, D. F. 1981, Clin. Toxicol., 18, 979.
52. Pederson, R. S., Olesen, A. S., Freund, L. G., Solgaard, P., and Larsen, E. 1978, Acta Med. Scand., 204, 429.
53. Rauws, A. G. and Vanheijst, A. N. P. 1979, Arch. Toxicol., 43, 153.
54. Lund, A. 1956, Acta. Pharmacol. Toxicol., 12, 260.