Nerve Conduction Studies in Chronic Arsenic Poisoning Patients

Soontorn Supapong MD, Msc*,
Kammant Phanthumchinda MD**, Jiruth Srirattanaban MD, MBA, PhD*

** Department of Preventive and Social Medicine, Faculty of Medicine, Chulalongkorn University*
*** Department of Medicine, Faculty of Medicine, Chulalongkorn University*

Objective : *To assess the nerve conduction functions among female patients with arsenical dermatoses compared with the controls.*
Design : *Cross-sectional analytic study.*
Subjects and Method : *Thirty females with skin lesions consistent with arsenical dermatoses and 27 controls who met the inclusion criteria were investigated by nerve conduction functions. Case findings resulted from a house-to-house survey in village12, Ronphibun subdistrict and village5, Saothong subdistrict, Nakhon Si Thammarat Province, southern Thailand in 1995.*
Results : *Differences between the arsenic-exposed population and the reference group regarding nerve conduction velocities (NCVs), proximal and distal latencies and amplitudes of sensory and motor nerve action potentials were not found except for the absent response to the sural nerve stimulation in three subjects of the exposed group.*
Conclusion : *The effects of arsenic toxicity on the peripheral nerves in the form of slow nerve conduction velocities were not found among female patients with arsenical dermatoses in Ronphibun. Some patients might have experienced arsenic neuropathy to some degree in the past (before 1987) but they had recovered to some degree at the time of the present investigation (1996) as most of the patients with chronic arsenic poisoning in the present study changed their sources of drinking water from arsenic-contaminated shallow-well water to other sources such as rainwater, tap water or commercial bottled water.*

Keywords : *Arsenic, Arsenical dermatoses, Neuropathy, Ronphibun, Nerve conduction velocities, NCVs*

J Med Assoc Thai 2004; 87 (Suppl 2): S207-12
e-Journal: *http://www.medassocthai.org/journal*

Peripheral neuropathy resulting from ingestion of arsenic compounds, especially a massive dose, has been recognised. Most of the arsenic neuropathy cases have come from acute exposures as the result of accidental or intentional ingestion[1]. Gastrointestinal symptoms, including nausea, vomiting and diarrhea, develop within minutes or hours after a single large dose of arsenic. Confusion, delirium, coma, circulatory collapse and death within 24 hours may occur among severe arsenic poisoning victims. If the patient survives, subacute effects of arsenic toxicity including hematological, dermatological and neurological effects will appear within seven days to three weeks. In terms of neurological effects, sensory symptoms may initially present as numbness, tingling sensations, and paresthesia in the distal parts of extremities. Hyperpathia, painful limbs and symmetrical muscular weakness in the extremities can be found. Foot and wrist drop is sometimes observed. Typically, arsenic neuropathy is a mixed motor-sensory polyneuropathy in which the sensory neuropathy is predominant[2]. Occasionally, some patients with arsenic intoxication may present with the Laundry-Guillain-Barr syndrome[3-5].

Although arsenic neuropathy is common among patients who ingest a massive dose of arsenic, it is of less concern among the subjects who use drinking-water containing appreciable amounts of arsenic [6]. It seems that there have been few studies concerning nerve conduction studies in persons exposed to inorganic arsenic via drinking water. In the present study, the authors applied nerve conduction studies to the villagers in Ronphibun, southern Thailand who drank arsenic-contaminated water for long periods and compared the results with those obtained from the controls. The aim of the present study was to detect subclinical neuropathy in chronic arsenic poisoning patients who had skin lesions consistent with the diagnosis of arsenical dermatoses.

Correspondence to : Supapong S. Department of Preventive and Social Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Subjects and Method

The protocol of the study was approved by the institutional ethical committee, Faculty of Medicine, Chulalongkorn University.

Arsenic exposed group

The group consisted of 30 females who were exposed to inorganic arsenic via drinking arsenic-contaminated shallow-well water (arsenic level >0.01 mg/l) and had skin lesions consistent with the diagnosis of arsenical dermatoses (hyperpigmentation on trunk or hyperkeratosis on palms and/or soles). Case findings resulted from a house-to-house survey in village12, Ronphibun subdistrict, Nakhon Si Thammarat Province, southern Thailand in 1995. Shallow wells this community were contaminated with arsenic which resulted from the past tin mining activities. The patients were admitted for the nerve conduction studies if they met the following selection criteria: They

1. were aged between 20 to 59 years old;
2. had resided in village 12, Ronphibun subdistrict for at least 10 years;
3. had never moved to other areas for more than one year;
4. had been diagnosed with arsenical dermatoses;
5. had not been exposed to neurotoxic agents which were mentioned as lead, mercury, manganese and organic solvents.
6. had never drunk alcohol or drank alcohol only on special occasions;
7. had never used opium, heroin, marihuana, or Kratom (an alkaloid which is a CNS stimulant);
8. had never had these diseases: diabetes mellitus, hypothyroidism, hyperthyroidism, stroke or physical injury to the nervous system.

Reference group

The group consisted of 27 females who drank water from a shallow well which had a low level of arsenic (WHO recommended level < 0.01 mg/l). These controls were selected from the results of a house-to-house survey in village5, Saothong subdistrict, Nakhon Si Thammarat Province, southern Thailand in 1995. They were admitted to the study if they met these criteria: They

1. were aged between 20 to 59 years old and were of similar age to a case in the exposed group;
2. had resided in village 5, Saothong subdistrict for at least 10 years;
3. had never moved to other areas for more than one year;
4. had no skin lesion consistent with the diagnosis of arsenical dermatoses;
5. had not been exposed to neurotoxic agents which were mentioned as lead, mercury, manganese and organic solvents;
6. had never drunk alcohol or drank alcohol only on special occasions;
7. had never used opium, heroin, marihauna, or Kratom;
8. had never had these diseases; diabetes mellitus, hypothyroidism, hyperthyroidism, stroke, or physical injury to the nervous system.

Tests for fasting blood glucose were performed in every subject. The persons who had fasting blood glucose levels higher than 120 mg% were excluded from the study. Blood tests were also measured for vitamin B1 (the erythrocytic transketolase activity (ETKA) and the thiamine pyrophosphate effect (TPPE). The persons who had ETKA less than 91 mmol/min/litre of red blood cell or TPPE more than 15%, were classified as having vitamin B1 deficiency and excluded from the study. The subjects' hair, nails and shallow-well water were collected and analysed for arsenic concentrations by the standard methods. Finally, the subjects were examined for their nerve conduction velocities (NCVs) at Songkhlanakarin Hospital, Songkhla province.

Nerve Conduction Study Method

The authors explained the details of the nerve conduction studies to every subject before the study was initiated. Informed consent was obtained from these subjects. Nerve conduction studies were performed on a Medelec® MS 96 machine by a well-trained technician supervised by a qualified Physical Medicine and Rehabilitation physician. The room temperature was kept at 26-28 C. Surface electrodes were used for both stimulating and recording purposes. A supramaximal stimulus with a duration of 0.1-0.2 msec and a strength of 100-300 V was delivered on each occasion. The motor nerve action potentials were obtained from the ulnar, peroneal and tibial nerves. The sensory nerve action potentials obtained from the ulnar and sural nerves were averaged 24-32 times.

Statistical analysis

Descriptive statistics were reported in terms of means, standard deviations and ranges. In order to test the mean differences between two independent samples, unpaired *t*-test was applied. A p-value of less than 0.05 was considered statistically significant.

Results

Table 1 presents means, standard deviations

Table 1. Means, standard deviations and ranges of arsenic level in shallow-well water, arsenic level in hair and arsenic level in nails obtained from the exposed and the reference populations

	Exposed group (n=30)	Reference group (n=27)
Age (years)	44.3	44.5
- SD	9.2	6.3
- Range	23-59	34-55
Arsenic level in shallow-well water (mg/litre)	1.000	0.002
- SD	1.080	0.001
- Range	0.040-3.318	ND*-0.004
Arsenic level in hair (mg/kg)	2.04	0.18
- SD	3.52	0.07
- Range	0.09-16.62	0.07-0.34
Arsenic level in nails (mg/kg)	2.53	0.58
- SD	3.64	0.34
- Range	0.40-17.51	0.12-1.55

*ND = non detectable (the detection limit in this laboratory is 0.0001 mg/l)

and ranges of arsenic level in shallow-well water, arsenic level in hair and arsenic level in nails obtained from the exposed and the reference populations. It was found that the average age of these two population groups was comparable (44.3 and 44.5 years for the exposed group and the reference group respectively). The controls were exposed to a low level of arsenic via drinking water (non detectable-0.004 mg/l) while the exposed group were exposed to a moderate to high level of arsenic via drinking water (0.040-3.318 mg/l). Arsenic exposures were confirmed by the measurements of arsenic concentrations in hair and nails. The average arsenic levels in hair and nails in the exposed group were higher than those in the reference group.

Table 2, Table 3 and Table 4 present means and standard deviations of nerve conduction velocities, latencies and amplitudes of the action responses of the peripheral nerves obtained from the exposed and the reference populations respectively. Means of NCVs were slower in the sensory ulnar, motor peroneal and motor tibial nerves in the exposed group, compared with the controls (Table 2). Means of NCVs were higher in the motor ulnar and sensory sural nerves in the exposed group, compared with the controls (Table 2). The differences of those mean NCVs between these two groups were minimal and were not statistically significant. It was noted that there was no response to the stimulations of the sural nerve in three subjects of the exposed group.

Mean proximal latency of the motor ulnar nerve, mean distal latency of the motor tibial nerve and mean distal latency of the sensory sural nerve in the exposed group were shorter than those in the reference group (Table 3). The other latencies in the exposed group were more prolonged than those in the reference group (Table 3). The differences of those mean latencies between these two groups were minimal and were not statistically significant.

Means of amplitudes were lower in the motor ulnar and the motor tibial nerves in the exposed group, compared with the controls (Table 4). Means of amplitude were higher in the sensory ulnar, motor peroneal and sensory sural nerves in the exposed group, compared with the controls (Table 4). The differences of those mean amplitudes between these two groups were minimal and were not statistically significant.

Table 2. Means and standard deviations of the NCVs (m/sec) of the peripheral nerves obtained from the exposed and the reference populations

Nerve	Exposed group (n=30)	Reference group (n=27)
Ulnar, motor	60.33 ± 3.93	59.52 ± 4.83
Ulnar, sensory	60.78 ± 6.55	61.77 ± 4.18
Peroneal, motor	48.04 ± 4.36	49.40 ± 3.71
Tibial, motor	48.49 ± 6.15	49.23 ± 5.13
Sural, sensory	45.47 ± 3.49 (n=27)	44.84 ± 3.55

Table 3. Means and standard deviations of the latencies (msec) of the peripheral nerves obtained from the exposed and the reference populations

Nerve	Exposed group (n=30)	Reference group (n=27)
Ulnar, motor		
Proximal latency	5.83 ± 0.49	5.96 ± 0.53
Distal latency	2.77 ± 0.37	2.71 ± 0.27
Ulnar, sensory		
Proximal latency	6.15 ± 0.70	6.09 ± 0.52
Distal latency	3.29 ± 0.29	3.26 ± 0.19
Peroneal, motor		
Proximal latency	10.12 ± 1.46	9.69 ± 0.94
Distal latency	3.93 ± 0.77	3.70 ± 0.54
Tibial, motor		
Proximal latency	10.93 ± 1.53	10.86 ± 1.35
Distal latency	4.17 ± 0.70	4.32 ± 0.65
Sural, sensory		
Distal latency	3.10 ± 0.28 (n=27)	3.14 ± 0.25

Table 4. Means and standard deviations of the amplitudes of the motor nerves (millivolts) and the sensory nerves (microvolts) obtained from the exposed and the reference populations

Nerve	Exposed group (n=30)	Reference group (n=27)
Ulnar, motor	6.57 ± 1.31	6.86 ± 1.33
Ulnar, sensory	15.42 ± 6.11	14.02 ± 5.01
Peroneal, motor	3.33 ± 2.00	3.16 ± 1.43
Tibial, motor	7.79 ± 4.30	8.01 ± 3.90
Sural, sensory	10.90 ± 7.53 (n=27)	10.41 ± 4.74

Discussion

From a house-to-house survey in village 12, Ronphibun subdistrict in 1995, 39 females aged between 20-59 years were found to have skin lesions which were compatible with the diagnosis of arsenic dermatoses and met the inclusion criteria. A simple random sampling method was applied to select 30 of 39 subjects to the nerve conduction studies. Thirty subjects in the reference group who met the inclusion criteria and had matched ages with those in the exposed group were invited to participate in the present study. Unfortunately, three subjects in the reference group refused to cooperate in the study. No one in both groups was excluded from the study because of having abnormal result of fasting blood glucose or blood tests for vitamin B1.

Factors which might influence the nerve conduction parameters were controlled as much as possible. Nerve conduction studies were performed by the same well-trained technician with the same equipment in the same room, in which the temperature was controlled to between 26-28 C. Height was associated inversely with NCVs[7]. In the present study, all subjects were females, so the variation of height among the subjects was not as great. In the present study, the average height of the subjects in the exposed group (151.70 cm) was comparable to that in the reference group (149.94 cm). No one in both groups had high alcohol consumption. The mean age of the subjects in the arsenic exposed group (44.27 years) was close to that in the reference group (44.48 years). It seems that the subjects in the present study were homogeneous in terms of age, height and alcohol consumption.

The controls lived in the area in which arsenic in the environment was low. The low arsenic concentrations in well-water (ranging from non detectable-0.004 mg/l), hair (ranging from 0.07-0.34 mg/kg) and nails (ranging from 0.12-1.55 mg/kg) of the subjects provided the evidence. The subjects in the exposed group lived in the arsenic-contaminated area, Ronphibun subdistrict. Ronphibun has been recognised as an arsenic contaminated area resulting from the past mining activities[8]. The high arsenic concentrations in well-water (ranging from 0.040-3.318mg/l), hair (ranging from 0.09-16.62 mg/kg) and nails (ranging from 0.40-17.51 mg/kg) of the subjects provided the evidence. Past arsenic exposure of the subjects in the exposed group was comfirmed by the presence of skin manifestations characteristic of chronic arsenic poisoning.

Arsenic neuropathy is commonly found among patients with acute arsenic poisoning resulting from ingestion of a massive dose of arsenic compounds. Peripheral neuropathy may be present in 10 days to three weeks after the acute exposure[9]. Typically, sensory nerves are markedly affected while motor nerves are moderately affected[2]. Sensory nerve action potentials and mixed compound nerve action potentials are absent in most of the severe cases[10]. The abnormalities of neurophysiological findings result from the destruction of myelins and axons[11]. The common electrophysiological findings are marked abnormalities of sensory nerve action potentials and mild reduction of motor nerve conduction velocities[10, 12].

There have been a few reports on arsenic neuropathy resulting from drinking arsenic-contaminated water[13-15]. Guha Mazumder (1998) reported 79 patients with clinical neuropathy who had been drinking arsenic-contaminated water in the endemic area of West Bengal, India[16]. Ten out of 29 patients who participated in the nerve conduction studies had abnormal nerve conduction velocities. One of the most quoted reports on nerve conduction studies in people who drink arsenic-contaminated water is the Hindmarsh et al's study in 1977. Their findings provided the evidence that prolonged exposure to arsenic via drinking arsenic-contaminated water would cause abnormal electromyographic results[17]. Hindmarsh et al commented that electromyography was a useful tool in the epidemiological assessment of chronic arsenic poisoning. Unfortunately, they did not compare the mean values of NCVs obtained from the arsenic-exposed subjects with those of the controls. Kreiss et al reported the contradictory results[18]. They could not find a dose-response relationship between arsenic ingestion and the abnormalities of nerve conduction velocities [18]. Means of nerve conduction velocities of four peripheral nerves were not significantly different among low, moderate and high arsenic-exposed groups. They proposed that duration, route of arsenic exposure and nutritional status might contribute to inconsistencies of findings among different populations[18].

In the present study, nerve conduction studies were performed in the subjects with skin lesions which were characteristic of chronic arsenic poisoning. The differences between the exposed population and the reference population in terms of nerve conduction velocities, proximal and distal latencies and amplitudes of sensory and motor nerve action potentials were not found except for the absent response to sural nerve stimulation in three subjects of the exposed group.

Classically, electrophysiological findings in acute arsenic neuropathy should resemble the findings found in axonal neuropathy in which the lower amplitudes of the action potentials are dominant. However, segmental demyelination might be found in acute arsenic neuropathy[19]. Segmental degeneration might have developed as a secondary phenomenon to axonopathy[12]. Among chronic arsenic poisoning cases, the recovery process of arsenic neuropathy could be found along the course of the disease. Regeneration of nerve fibres might occur [20]. Therefore, the electrophysiological findings among chronic arsenic neuropathy patients may be varied (may not be typical finding of axonopathy).

In a situation like Ronphibun, some patients might have experienced arsenic neuropathy to some degree in the past (before 1987) but had recovered to some degree at the time of the present investigation (1996). Although four subjects in the exposed group had hyporeflexia, there was no past medical history of polyneuropathy among them. Concerning arsenic exposure, most of the patients with chronic arsenic poisoning in the present study changed their sources of drinking water from arsenic-contaminated shallow-well water to other sources such as rainwater, tap water or commercial bottled water about nine years ago. However, the villagers in this community have been exposed to arsenic via the food chain but the concentration of arsenic may not be high compared to the exposure via drinking water. In addition, it seems that the course of arsenic neuropathy might have varied among the subjects in Ronphibun. In the cross-sectional study design, subjects with different courses of disease could not be differentiated.

In summary, the effects of arsenic toxicity on the peripheral nerves in the form of slow nerve conduction velocities were not found among female patients with arsenical dermatoses in Ronphibun. Further study in populations with current exposure to arsenic via drinking-water should be carried out to ascertain whether ingestion of inorganic arsenic at levels of higher than 0.01 ppm in drinking water can cause peripheral neuropathy.

Acknowledgements

The authors wish to thank the staffs of Hatyai Hospital and Songklanakarin Hospital for their cooperation and helping in the clinical laboratory investigations. We also wish to thank Dr Dipankar Chakraborti and his colleagues in Jadavpur University, India for arsenic analysis of hair and nail samples, and scientists at the Medical Science center, Songkla Province for arsenic analysis of water samples.

This study was supported by the Rachadapisek Sompoj China Medical Board Funds, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

References

1. Windebank AJ. Specific inhibition of myelination by lead vitro; comparison with arsenic, thallium and mercury. Exp Neurol 1996; 94: 203-12.
2. Oh SJ. Clinical eletromyography: Nerve conduction studies, 2nd ed. Baltimore: Williams & Wilkins; 1993.
3. Wilbourn A, Roger L, Salanza V. Acute arsenic intoxication producing a segmental demyelinating polyradiculoneuropathy. Muscle & Nerve 1983; 6: 533.
4. Donofrio PD, Wilbourn AJ, Albers JW, Rogers L, Salanga V, Greenberg HS. Acute arsenic intoxication presenting as Guillain-Barr -like syndrome. Muscle & Nerve 1987; 10: 114-20.
5. Goddard MJ, Tanhehco JL, Dau PC. Chronic arsenic poisoning masquerrading as Landry-Guillain-Barr syndrome. Electromyogr Clin Neurophysiol 1992; 32: 419-23.
6. WHO. Arsenic and arsenic compounds. Environmental Health Criteria 224, 2nd ed. Geneva, World Health Organization; 2001.
7. Campbell WW, Ward C, Swift TR. Nerve conduction velocity varies inversely with height. Muscle & Nerve 1981; 4: 520-3.
8. Chopraprawon C, Rodcline A. Chronic arsenic poisoning in Ronphibool Nakhon Sri Thammarat, the Southern Province of Thailand. In: Abernathy CO, Calderon RL & Chappell WR, eds. Arsenic exposure and health effects. London, Chapman & Hall; 1997: 69-77.
9. Winship KA. Toxicity of inorganic arsenic salts. Adv Drug React Ac Pois Rev 1984; 3: 129-60.
10. Le Quesne PM, McLeod JG. Peripheral neuropathy following a single exposure to arsenic. Clinical course in four patients with electrophysiological and histological studies. J Neurol Sci 1977; 32: 437-51.
11. Heyman A, Pfeiffer JB, Jr, Willett RW, Taylor HM. Peripheral neuropathy caused by arsenical intoxication. A study of 41 cases with observations on the effects of BAL (2,3-dimercaptopropanol). New Engl J Med 1956; 254: 401-9.
12. Murphy MJ, Lyon LW,Taylor JW. Subacute arsenic neuropathy: clinical and electrophysiological observations. J Neurol Neurosurg Psychiatry 1981; 44: 896-900.
13. Feinglass EJ. Arsenic intoxication from well water in the United States. N Engl J Med 1973; 268: 828-30.
14. Franzblau A, Lilis R. Acute arsenic intoxication from environmental arsenic exposure. Arch Environ Health 1989; 44: 385-90.

15. Wagner SL, Maliner JS, Morton WE, Braman RS. Skin cancer and arsenic intoxication from well water. Arch Dermatol 1979; 115: 1205-7.
16. Guha Mazumder DN, Das GJ, Santra A, Pal A, Ghosh A, Sarmar S. Chronic arsenic toxicity in West Bengal - The worst calamity in the world. J Indian Med Assocn 1998; 96: 4-7.
17. Hindmarsh J, McLetchie OR, Heffernan LPM, Hayne OA, Ellenberger HA, McCurdy RF, Thiebaux HJ. Electromyographic abnormalities in chronic environmental arsenicalism. J Anal Toxicol 1977; 1: 270-6.
18. Kreiss K, Zack MM, Landrigan PJ, Feldman RG, Niles CA, Chirico-Post J, Sax DS, Boyd MH, Cox DH. Neurologic evaluation of a population exposed to arsenic in Alaskan well water. Arch Env Health 1983; 38: 116-21.
19. Chhuttani PN, Chopra JS. Arsenic poisoning. In: Vinken PJ & Bruyn GW, ser eds. Handbook of clinical neurology, Vol 36: Vinkin PJ, Bruyn GW, Cohen MM & Klawans HL, vol eds. Intoxication of the nervous system, part I. Amsterdam: North-Holland Publishing Co; 1979: 199-216.
20. Goebel HH, Schmidt PF, Bohl J, Tettenborn B, Kramer G, Gutmann L. Polyneuropathy due to acute arsenic intoxication: biopsy studies. J Neuropathol Exp Neurol 1990; 49: 137-49.

การศึกษาการชักนำประสาทในคนไข้พิษสารหนูเรื้อรัง

สุนทร ศุภพงษ์, กัมมันต์ พันธุมจินดา, จิรุตม์ ศรีรัตนบัลล์

วัตถุประสงค์ *: เพื่อประเมินการชักนำประสาทในคนไข้เพศหญิงที่มีอาการแสดงทางผิวหนังจากพิษสารหนูเรื้อรัง โดยเปรียบเทียบกับกลุ่มควบคุม*

รูปแบบการวิจัย *: การศึกษาเชิงวิเคราะห์แบบตัดขวาง*

ประชากรและวิธีการศึกษา *: คนไข้เพศหญิงที่มีอาการแสดงทางผิวหนังจากพิษสารหนูเรื้อรัง จำนวน 30 คน และกลุ่มควบคุม จำนวน 27 คน ที่ตรงกับเกณฑ์การคัดเลือกเข้าศึกษา ได้รับการศึกษาการชักนำประสาท โดยประชากรในกลุ่มศึกษา และกลุ่มควบคุมได้จากการสำรวจชาวบ้านในหมู่ที่ 12 ตำบลร่อนพิบูลย์ และหมู่ที่ 5 ตำบลเสาธง อำเภอร่อนพิบูลย์ จังหวัดนครศรีธรรมราช ในปีพุทธศักราช 2538*

ผลการศึกษา *: ไม่พบความแตกต่างของค่าเฉลี่ยความเร็วชักนำประสาท เวลาชักนำประสาทส่วนต้นและส่วนปลาย และความสูงของคลื่นประสาท ทั้งเส้นประสาทรับความรู้สึก และเส้นประสาทสั่งการ ของกลุ่มที่ศึกษาและกลุ่มควบคุม ยกเว้นการตรวจไม่พบการตอบสนองต่อการกระตุ้นของเส้นประสาทซูรัล ในตัวอย่าง 3 รายในกลุ่มที่สัมผัสสารหนู*

สรุป *: การศึกษานี้ไม่พบการเปลี่ยนแปลงของความเร็วชักนำประสาทในคนไข้เพศหญิงที่อยู่ในตำบลร่อนพิบูลย์ที่มีอาการแสดงทางผิวหนังจากพิษสารหนูเรื้อรัง คนไข้อาจจะเคยมีความผิดปกติของระบบประสาทส่วนปลายในอดีต (ก่อนปี พ.ศ. 2530) แต่หลังจากหยุดดื่มน้ำที่มีสารหนูปนเปื้อนแล้ว ความผิดปกตินั้นได้หายไป ณ เวลาที่ได้ทำการศึกษา (ปี พ.ศ. 2539)*