

Reappraisal of somatosensory disorders in methylmercury poisoning

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Abstract

The first well-documented methylmercury (MeHg) poisoning by consumption of fish arose in Minamata, Japan in 1953. MeHg had dispersed from Minamata to the Shiranui Sea. The temporal changes in MeHg in the umbilical cords indicate that residents living around that Sea had been exposed to low-dose MeHg through fish consumption for about 20 years (at least from 1950 to 1968). They have complained of paresthesia at the distal parts of the extremities and around the lip even 30 years after the cessation of exposure to anthropogenic MeHg. The thresholds of touch and two-point discrimination of those residents and Minamata disease (MD) patients were examined using the quantifiable instruments. They could perceive the stimulation of touch although their touch thresholds significantly increased in comparison to those of the control people. Their touch thresholds increased at the proximal extremities and the trunks as well as at the distal extremities. The evenly distributed increases at both distal and proximal parts revealed that the persistent somatosensory disturbances were not caused by the injuries to their peripheral nerves. The thresholds of two-point discrimination, which are associated with the function of the somatosensory cortex, increased at both forefingers and the lip in both groups. Taking into consideration that, the apraxia limb kinetics, astereognosis and disorder of active sensation, which are all associated with damage to the somatosensory cortex, were detected, it is proposed that the persisting somatosensory disorders after discontinuation of exposure to MeHg were induced by diffuse damage to the somatosensory cortex.

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Keywords: Methylmercury poisoning; Minamata disease; The somatosensory cortex; Touch thresholds; Two-point thresholds

1. Introduction

Environmental mercury levels have increased considerably since the on-set of the industrialized age [46]. Once deposited, the mercury form can change from inorganic to MeHg, which would be condensed through food chain, especially in fish. MeHg readily passes through the placental and blood–brain barriers, and has highly toxic effects on the human brain [54]. MeHg has a relatively long biological half-life in humans. Half-life is usually

estimated as an average of 70 days [54]. Therefore, MeHg accumulates substantially into the human brain causing irreversible damage as a result of long retention time. Exposure to low-dose MeHg through fish consumption causes adverse effects on the developing brain as well as the adult brain [16,27,37]. Effects of long-term exposure to MeHg on the human brain are the present global problem.

The first mass MeHg poisoning by consumption of contaminated fish occurred in Minamata, Japan, in 1953 (Fig. 1). Then it was called Minamata disease [42]. MeHg chloride, which was produced as a by-product in the acetaldehyde plant of the factory in Minamata [22], was first discharged to Minamata Bay and subsequently to

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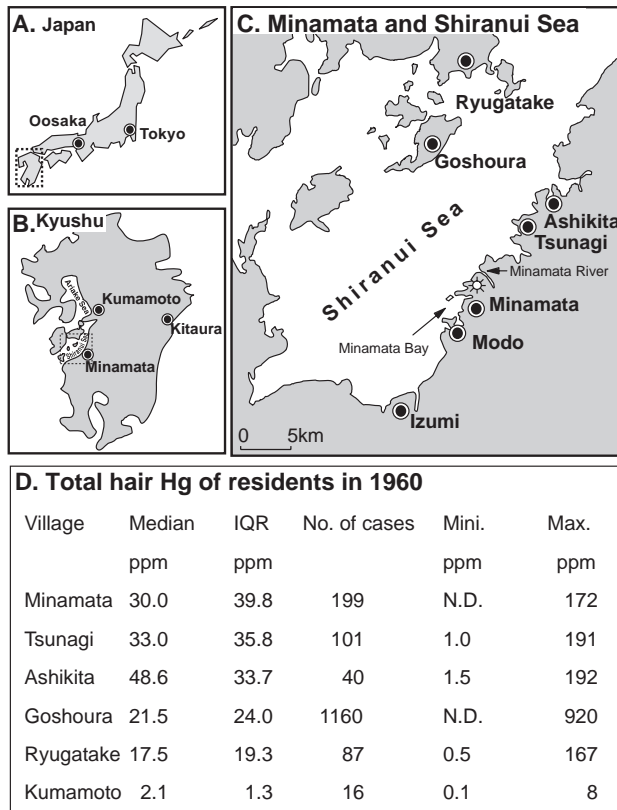


Fig. 1. T-Hg concentrations in hairs of residents on the coast of the Shiranui Sea in 1960 (C, D). The map of Japan (A) and Kyushu Island (B). Minamata is located on the coast of the Shiranui Sea in the Kyushu Island, the southern part of Japan (A, B, C). The area of Minamata Bay and the Shiranui Sea was about 2 km² and 1200 km², respectively. Anthropogenic MeHg pollution had extended from Minamata Bay and Minamata River to all over the Shiranui Sea [35]. The local government of Kumamoto Prefecture investigated T-Hg levels in hairs of 1644 residents on the coast of Shiranui Sea in 1960 [11]. We summarized the individual data of T-Hg values in their hairs (D). Median and interquartile range (IQR) were calculated. N.D.: none detected.

Minamata River until 1968, which led to the pollution of the surrounding inland sea of Shiranui Sea (Fig. 1) [25,35]. The fish and shellfish in these areas contained MeHg combined with sulphur-containing amino acids of protein [42].

Exposure to a high level of MeHg through the consumption of those fish caused severe neuron loss in the cerebral cortex and cerebellum in early acute adult cases of MD [42]. The following disorders were observed: the blurred vision, associated with constriction of visual field caused by damage to the primary visual area of the occipital lobe; a hearing impairment caused by damage to the primary auditory area in the temporal lobe; a somatosensory disorder. The lesion of somatosensory disorder has not been cleared. Ataxic gait, clumsiness of the hands, dysarthria were said to be associated with cerebellar damage. Tendon reflexes were usually preserved or even become hyperactive in the earlier-seen severe cases of MD patients. In addition to this, in children born of the

mothers who were exposed to MeHg, an extensive spongiosis of the cerebral cortex was seen. This became a characteristic feature of fetal MD. Thus, MeHg became known to be highly neurotoxic to human brain, especially human developing brain.

The discharge of a high level of MeHg into Minamata Bay caused severe MeHg poisoning cases around Minamata Bay from 1953. Later in 1958, since the factory changed its drainageway to Minamata River [25], similar severe cases of MeHg poisoning had expanded to the fishing villages along the coast of the Shiranui Sea in 1959. The median value of T-Hg in hairs of 1644 residents was 23.4 ppm (range N.D.–920 ppm) in 1960 [13]. Fig. 1D shows that the mercury concentrations in the hairs of residents on the coast of the Shiranui Sea were about 10–20 times higher than those of non-polluted people in Kumamoto Prefecture in 1960.

Families in Japan have maintained the tradition of keeping a small piece of the umbilical cords in memory of giving birth to a baby. The umbilical cords of Minamata residents have been known as a biological marker of MeHg pollution [2,19,36]. Fig. 2 shows the temporal changes in MeHg concentrations in the umbilical cords of the 68 residents living around the Shiranui Sea excluding those from Minamata city. It is reported that MeHg concentrations in the umbilical cords of inhabitants of Tokyo were 0.11 ± 0.03 (Mean \pm SD) ppm in 1975 [19,36]. In the area around the Shiranui Sea, the umbilical cords which contained more than 0.2 ppm of MeHg were detected until 1968, when the factory allegedly stopped production of acetaldehyde (Fig. 2) [2,36]. Because a ban on commercial fishing has never been placed in the Shiranui Sea, inhabitants of that coastal area, whose diet was heavily dependent on locally caught fish, were suspected to be exposed to MeHg with the consumption of polluted fish for almost 20 years (1950–1968). After data on levels of T-Hg in hairs of these individual residents became available in 1970, several research groups including us started to do epidemiological investigations concerning effects of long-term exposure to MeHg.

Part of our studies has already showed that hypoaesthesia was detected in more than 70% of the residents of Goshoura in the 1970s [35]. Goshoura is a town on an island located on the opposite shore from Minamata in the middle of the Shiranui Sea (Fig. 1). These people still have a sensory disorder 30 years after the cessation of MeHg exposure. When they were examined with conventional sensory examinations using a painting brush and pinprick, they reported the sensory reduction at the distal extremities, in the pattern of the so-called “stocking–glove distribution”, which is a characteristic feature of the peripheral neuropathy. Then it has been believed that this sensory disorder was a symptom of damage to peripheral nerves, leading to a diagnosis of the peripheral neuropathy.

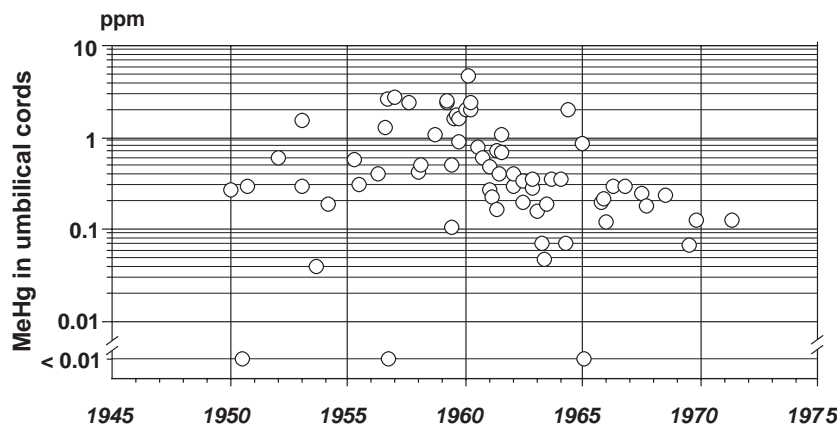


Fig. 2. The temporal changes in MeHg concentrations in the umbilical cords of 68 residents living around the Shiranui Sea (Izumi; 37, Ashikita; 14, Tsunagi; 10, Goshoura; 7, Fig. 1) from 1950 to 1971. Each open circle indicates the individual value of MeHg in the umbilical cords. The umbilical cords which contained more than 0.2 ppm of MeHg were detected until 1968, when the factory allegedly stopped production of acetaldehyde [2,36]. The mean of MeHg concentrations in the umbilical cords of 24 inhabitants of Tokyo was 0.11 ± 0.03 (Mean \pm SD) ppm in 1975 [19,36]. The individual data were kindly provided by Dr. M. Harada.

In case of MeHg poisoning in rats, studies clarify that the neurological effects of MeHg is damage to the peripheral sensory nerves and/or the dorsal root ganglion [53,56]. These observations on MeHg poisoning in rats were conveniently extrapolated to MD patients without control studies [14,33]. However, definitive scientific data on damage to human peripheral nervous system by MeHg have not been reported [55].

In pathological examinations of the early MD patients in the 1950s, damage to the peripheral nervous system was not detected [42]. Nagaki et al. performed electrophysiological and histopathological studies on sural nerve of MD patients in comparison with control people in 1985 [34]. No differences between MD patients and control people were reported. In addition, Tokuomi et al. examined short-latency somatosensory evoked potentials (SSEP) in MD patients more than 10 years after the cessation of exposure to MeHg, and clarified that lesion of persistent sensory disorder in MD patients is in the somatosensory cortex, but neither the peripheral nerves nor the spinal cord nor the thalamus [45]. So these results suggest that the persistent sensory disorder in MD patients is not caused by injuries to the peripheral nerves. Then, there has been confusion about the lesion of the persistent sensory disorder in human MeHg poisoning.

It is known that diminution or loss of tendon reflexes is an invariable sign of peripheral nerve disease [26,28,39]. Yet, tendon reflex of people in Goshoura, who have complained of paresthesia at the distal parts of the extremities, were often preserved. Therefore, it is questioned whether their disorders were caused by injuries to their peripheral nerves.

Here we propose that central and not peripheral mechanisms are involved in MeHg poisoning. So as to clarify this hypothesis, we examined the thresholds of touch and two-point discrimination of both cases of Goshoura and MD using the quantifiable instruments.

2. Materials and methods

2.1. Study design

In Japan, there are following two terms used separately: MD and MeHg poisoning. MD, certainly, is a form of MeHg poisoning. Even so, to be MD patients, people who were affected by MeHg have to apply to the local government for the official recognition of their suffering. Once they are certified as MD patients according to the Diagnostic Guidelines for MD, they would be eligible for compensation [43]. The Diagnostic Guidelines for MD were developed for the compensation scheme under the Law Concerning Special Measures for the Relief of Pollution-related Health Damage, which was put into effect since 1969. Provided that the coastal areas around the Shiranui Sea had a population of about 200,000 in 1960 [18], it is estimated that people in the order of 200,000 were to be those suspected cases of MeHg poisoning. In spite of this, only about 17,000 of them had applied for the certification, and among them 2265 were authorized [49].

In the present study, those suspected cases of MeHg poisoning and age-matched control people were examined at first. Then, MD patients were studied likewise, but in more detailed way. As suspected cases, 32 residents of Goshoura were studied. Goshoura is a fishing town, and most of the fishermen there went fishing all over the inland sea of Shiranui Sea to catch mainly sardines by the purse seiner [35]. Part of their catch was brought back to be shared in the communities. At that time in 1950s, they used to consume about 500 g of fish, which consisted of small sea fish like sardines and horse mackerels on the whole, per day. According to the report of Kumamoto Prefectural Institute of Public Health, the median of hair T-Hg concentrations of 1160 cases in Goshoura town was 21.5 ppm (range N.D.–920 ppm) [11], while the median value of that of non-polluted Japanese was 2.1 ppm (range

0.1–7.5 ppm) in 1960 [42] (Fig. 1). The median concentration of T-Hg in the hairs of the cases examined in this report was 37.0 ppm (range 10.0–75.0 ppm) in 1960 and 2.4 ppm (range 0.6–5.0 ppm) in 2002 (Table 2). Their mean age was 66.4 ± 12.5 (Mean \pm SD).

Fifty-three people in Kitaura were examined as a control group. Kitaura is a fishing town as well, located on the eastern coast of Kyushu Island. In this area of eastern coast, there was no history of aquatic pollution by anthropogenic MeHg. Fishermen in Kitaura mostly catch coastal fish in Hyuganada, where the mean value of T-Hg in fish was 0.11 ± 0.07 mg/kg in 1971 [23]. Similarly, a share of a catch of fish forms an important part of their diet. The median concentration of T-Hg in hairs of the residents was 2.8 ppm (range 0.9–9.2 ppm) in 2002 (Table 2). The mean age of persons examined was 68.6 ± 6.5 (Mean \pm SD).

In case of probing of three MD patients, three persons in Kitaura were set as a control group. Table 1 shows the detail of the three formally-admitted MD cases. Case 1 is a man aged 77 and had been engaged in fishery around 1960 in Ashikita (Fig. 1), a town north of Minamata. His hair T-Hg levels were 64.5 ppm in 1960. Case 2 is a man aged 78 and had been working as a fisherman and a shipwright in the place called Modo (Fig. 1), where many severe cases of MeHg poisoning were found in the early days. His hair T-Hg levels were 38.5 ppm in 1960. Both of them had been exposed to MeHg in their 30s–40s. Case 3, a son of Case 2 is 45 years old. His T-Hg concentrations in hair were 59 ppm at the age of 3 (1959) and 12 ppm at 7 (1963). He had been exposed to MeHg not only at the fetal stage but at the neonatal stage as well [42].

Our purposes of medical examinations were informed to all subjects [35]. All cases giving informed consent were examined at the community centre or their own houses.

Table 1
Individual data on three MD patients

	Sex	Year of birth	Age ^a	Place of residence	T-Hg ^b in hairs	
Case 1	Male	1923	77	Ashikita	64.5	
Case 2	Male	1922	78	Modo	38.5	
Case 3	Male	1956	45	Modo	59.0	
Control			77 ± 10^c	Kitaura	ND ^d	
Two-P ^c	R13 (mm)	L13 (mm)	R12 (mm)	L12 (mm)	Lip (mm)	Tongue (mm)
Case 1	6	7	6	7	9	5
Case 2	5	5	6	5	4	3
Case 3	7	6	8	7	7	3
Control	3.3 ± 0.6	3.7 ± 0.6	4.3 ± 0.6	4.3 ± 0.6	2.3 ± 1.2	2.0 ± 0.0

^a Three MD patients and three Kitaura subjects were examined in 2001.

^b T-Hg concentrations in hairs were examined in 1959 or 1960.

^c Mean \pm SD.

^d T-Hg concentrations in hairs of Kitaura subjects were not examined in 1960.

^e The threshold of two-point discrimination. R13 and L13 indicate the right and left forefinger, respectively. R12 and L12 indicate the right and left thumb, respectively.

2.2. Sensory measures

When Goshoura residents were examined with conventional sensory tests using a painting brush and pinprick formerly they reported the sensory reduction at the distal extremities, in the pattern of the so-called “stocking–glove distribution”: their reports, however, were often variable. Their variable reports made it difficult for us to localize sensory disorders in discrete areas of the body. The sensory examinations were conducted at the participant’s village so that the tester knew that the participant in Goshoura was a suspected case of MeHg poisoning. Therefore, the quantifiable methods were used for more precise test, not to be influenced by preconceptions about the subjects.

2.2.1. Touch thresholds

Touch thresholds were measured with the Semmes–Weinstein pressure aesthesiometer, a set of modified von Frey-type filaments [9,40,52]. Twenty nylon filaments, equal in length (38 mm) but varying in diameter (0.06–1.14 mm), were each implanted at one end of a plastic rod. These filaments are calibrated to provide a specified force measured in grams and are identified by a number that is 10 times the log of the force in milligram exerted at the tip of the filament (e.g. the 5.07 monofilament exerts 11.70 g of force) [40]. When the subjects were examined, they were shown the filaments, and told that they would be touched with some of them in order to determine the lightest pressure they could perceive. During testing, they lay on their back, and kept their eyes closed to eliminate any visual cues produced by the movements of the experimenter. Each contact was applied for about 1 s with intervals of about 3–8 s between applications. The filaments were applied in serial order, starting from different points below and above the expected thresholds. The subjects were instructed to say “yes” immediately upon feeling the tip of one of these touches. Three replies at the same limit were required for the determination of thresholds by the experimenter.

We measured the touch thresholds of residents of Goshoura and Kitaura at the pads of the distal phalanges of forefingers, the center of the midline of volar forearms, the breasts (5 cm below the clavicles on the midclavicular line) and the center of nonpigmented lower lip [52].

Then, we examined the touch thresholds at 13 body regions of each side in three MD patients and three Kitaura residents. These 13 body parts in one side were selected according to the report of Weinstein [52]. Examined body regions were the following: 1. the volar surface of hallux, 2. the volar surface of sole, 3. the dorsal surface of calf, 4. the dorsal surface of thigh, 5. the dorsal surface of shoulder, 6. breast, 7. nonpigmented lower lip, 8. forehead, 9. shoulder, 10. upperarm, 11. forearm, 12. thumb, and 13. forefinger (Fig. 5G). Among them, the 6. breast, the 7. nonpigmented lower lip, the 11. forearm and the 13. forefinger are the same body parts as examined in Goshoura residents. More than 3 h were required for the examination of these 26 body parts

in both sides. To keep their concentration, several times of rests were taken.

2.2.2. Thresholds of two-point discrimination

In the measurement of thresholds of two-point discrimination, the ability to distinguish two points from one was tested by using an adjustable compass or the Disk-Criminator [9,11,41,51]. The smallest distance between two points at which they are still perceived as two separate contacts is the thresholds of two-point discrimination. When the subjects were examined, they were shown the instrument and told that a part of their body would be touched sometimes with two points and sometimes with only one. Then, they were instructed to say “one” immediately upon feeling of one point, or “two” upon feeling of two points. During testing, they lay on their back, and kept their eyes closed to eliminate any visual cues produced by the movements of the experimenter. Care was taken to apply the compass points with firm and equal pressure; in every instance, the pressure was well above the subject’s pressure sensitivity. The sequence of application of one or two points was random. Three correct answers at the minimum distance were required for the determination of thresholds by the tester. In the testing of people in Goshoura and Kitaura, at the pads of the distal phalanges of forefingers and the center of nonpigmented lower lip were measured. In the case of three MD patients and three Kitaura residents, the pads of the distal phalanges of forefingers, the pads of the distal phalanges of thumbs, the center of nonpigmented lower lip and the tip of tongue were examined.

2.3. T-Hg concentrations in hair

2.3.1. T-Hg concentrations in hairs of residents of Goshoura and MD patients in 1960

Doi and Matsushima examined T-Hg levels in hairs of 1644 residents on the coast of the Shiranui Sea in 1960 [13]. Individual T-Hg values of sixteen cases of Goshoura subjects and two MD patients were obtained from their data. T-Hg value of Case 3 was taken from the report by Study Group of Minamata disease [42]. The median and interquartile range (IQR) of values of T-Hg in hairs was calculated (Fig. 1D).

2.3.2. T-Hg concentrations in hairs of Goshoura and Kitaura residents in 2002

The levels of T-Hg in hairs were measured by a cold vapor atomic absorption spectrometry according to Akagi’s method [1]. Twenty-three hair samples from persons in Goshoura and twenty-five hair samples from persons in Kitaura were analyzed.

2.4. Statistical analysis

The median and IQR of values of T-Hg in hairs was calculated. In the statistical analysis of the touch thresholds

at 7 body regions of both Goshoura and Kitaura residents, an analysis of variance with repeated measures was used. The differences of the thresholds of two-point discrimination between both groups were tested for significance using nonparametric test (Mann–Whitney *U* test) since *F*-test revealed that the variances were unequal. All statistical analyses were conducted with StatView J version 4.11 for Macintosh [20].

3. Results

3.1. Assessment of the touch thresholds in residents of Goshoura

The forehead and the lip are innervated by the trigeminal nerve and the upper extremities and breast are innervated by the cervical or thoracic spinal nerves. Residents of Goshoura could perceive the stimulation of touch although their touch thresholds were significantly higher than those of the control people. Their touch thresholds increased not only at the distal extremities but also at the proximal extremities and the trunks (Fig. 3). An analysis of variance with

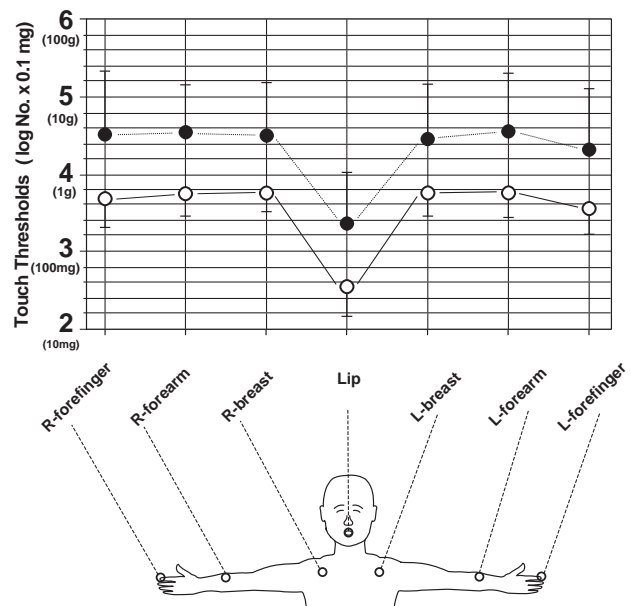


Fig. 3. The thresholds of touch in Goshoura subjects (closed circle) and Kitaura subjects (open circle). The touch thresholds at forefinger, forearm and breast of both sides, and the tip of lower lip were examined. An analysis of variance with repeated measures showed that there were not significant interactions between the villages and the thresholds ($p=0.9148$). This result suggests that all thresholds were shifted by the same amount. The between-group main effect for touch thresholds is significant ($p<0.0001$). The within-subject main effect for touch thresholds is also significant ($p<0.0001$). Each point represents the mean. Vertical bars express SD of the mean. These results clarified that touch thresholds of MeHg poisoning patients evenly increased at any regions examined. The even increases of the thresholds at the distal and proximal regions are not characteristic in the peripheral neuropathy, in which the distal parts of the limbs are said to be more affected than the proximal [7,15,44,50].

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3.2. Assessment of the thresholds of two-point discrimination in residents of Goshoura

Goshoura cases could perceive the stimulation of one point. And they could recognize the duality of two points even at a small distance when two points are applied successively. The thresholds of two-point discrimination in the right and left forefinger of Kitaura cases were 3.6 and 3.6 mm, respectively. These values were comparable to those of normal old people reported by D.S. Loui et al. and J.C. Stevens [29,41]. The thresholds of two-point discrimination in the forefingers and the lip of Goshoura subjects were about two times as high as those of the control people (Fig. 4). The laterality was not observed in

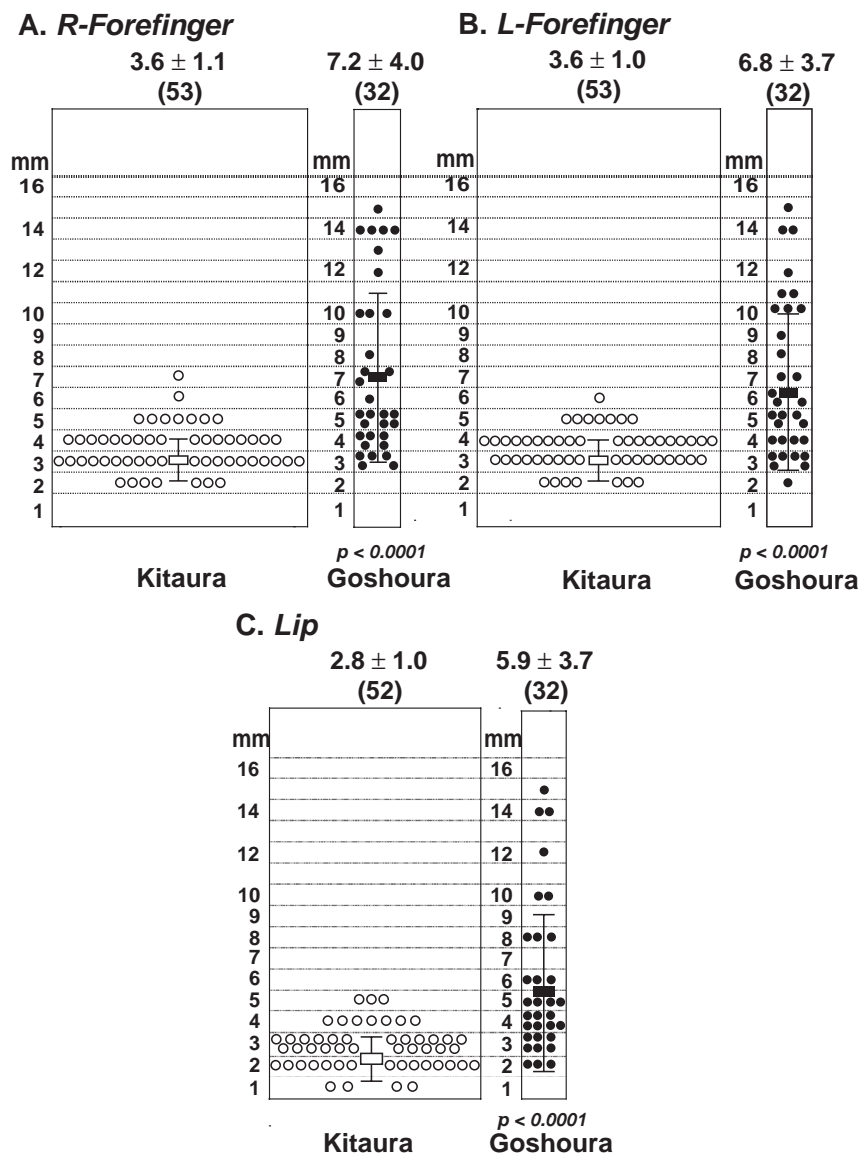


Fig. 4. The thresholds of two-point discrimination in Goshoura subjects (closed circle) and Kitaura subjects (open circle). Both forefingers and the tip of lower lip were examined. Each point represents the threshold of two-point discrimination in the individual residents examined. The mean is indicated by a rectangle. Vertical bars express SD of the mean. *Mean±SD (the number of people examined). The variance of group, mean and SD were calculated by *F*-test. The differences of the thresholds of two-point discrimination between groups were tested for significance using nonparametric test (Mann–Whitney *U* test) since *F*-test revealed that the variances were unequal. * $p<0.0001$.

the same way as in the results obtained from the test of the touch thresholds.

3.3. Assessment of the touch thresholds in MD patients

The modality of touch was preserved in all cases of MD patients. The increases of the touch thresholds were detected

at the lower extremities, the trunk as well as the upper extremities and the face of any MD patients (Fig. 5). These increases in MD patients were not restricted to the distal extremities as generally believed as the stocking-glove type. These results also suggest that the persistent somatosensory disorders in MD patients are not caused by injuries to peripheral nerves.

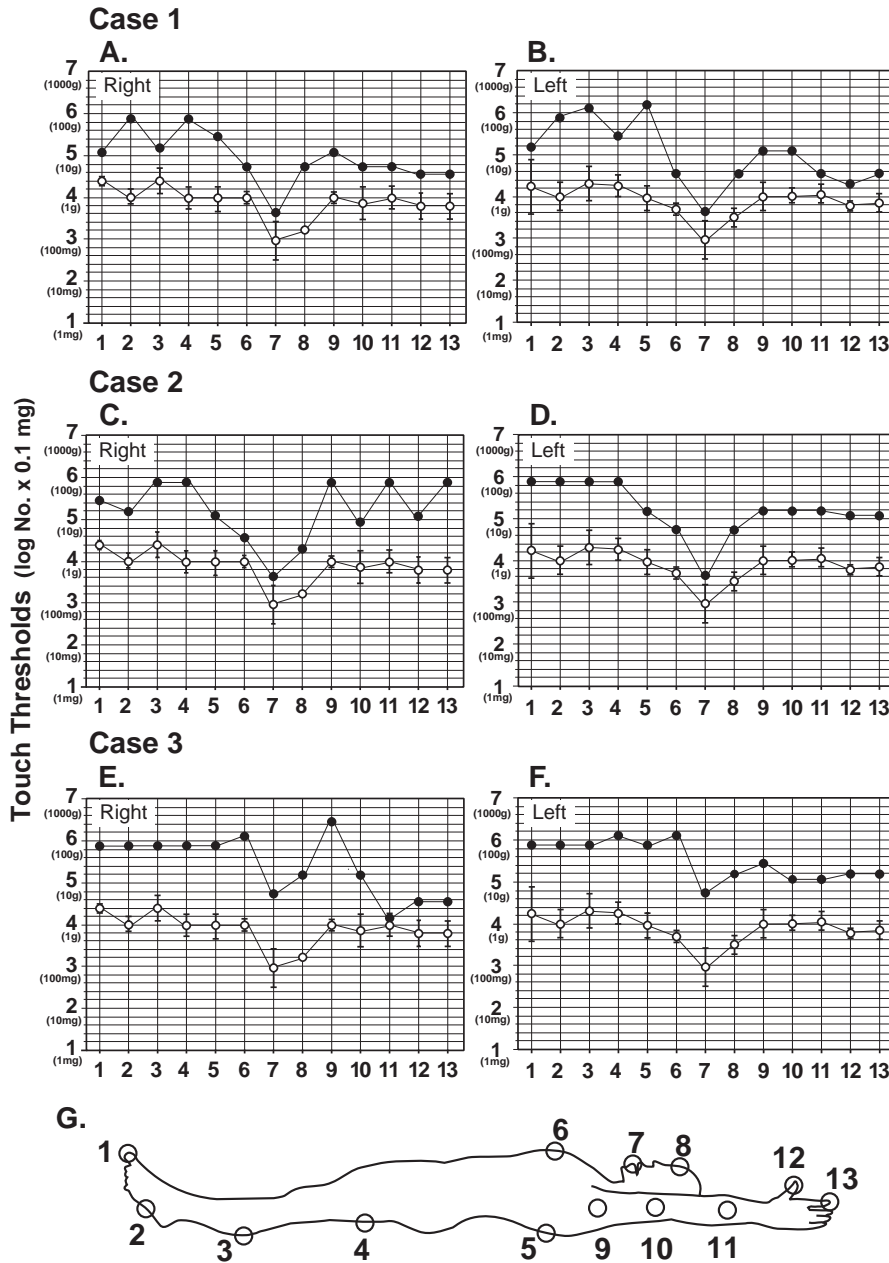


Fig. 5. The thresholds of touch in MD patients (closed circle) and Kitaura residents (open circle). Systemic increases of touch thresholds were observed in MD patients. (A), (B) Results of case 1. (C), (D) Results of case 2. (E), (F) Results of case 3. Each point of open circle represents the mean of thresholds of touch in 3 Kitaura subjects. The control values are the same in all panels. (G) Thirteen body regions were selected according to the report of S. Weinstein [52]. Examined body regions were the following: 1. the volar surface of hallux, 2. the volar surface of sole, 3. the dorsal surface of calf, 4. the dorsal surface of thigh, 5. the dorsal surface of shoulder, 6. breast, 7. nonpigmented lower lip, 8. forehead, 9. shoulder, 10. upperarm, 11. forearm, 12. thumb, and 13. forefinger. Vertical bars express the standard error of the mean.

3.4. Assessment of the thresholds of the two-point discrimination in MD patients

On the one hand, the increases of the thresholds of two-point discrimination in MD patients were detected in the thumbs and the tongue as well as the forefingers and the lip (Table 1). On the other hand, the increases of thresholds in the forefingers and the lip of MD patients were comparable to those of Goshoura residents (Table 1, Fig. 4). On the whole, MeHg poisoning would cause damage to a wide area of the somatosensory cortex.

4. Discussion

The discharge of MeHg to the Minamata Bay first caused severe cases of MD, and its discharge then to the Minamata River caused MeHg poisoning in residents on the coast of the Shiranui Sea [35]. Fig. 1 shows that anthropogenic MeHg pollution was dispersed all over the Shiranui Sea [25,35]. Fig. 2 shows that residents living around the Shiranui Sea were suspected to be exposed to MeHg until 1968, when the factory allegedly stopped production of acetaldehyde [2,36]. Taking these into consideration, those residents were supposed to be exposed to MeHg of anthropogenic origin for about 20 years (at least from 1950 to 1968).

The median concentration of T-Hg in hairs of Goshoura cases, who were examined in this report, was 37 ppm (range N.D.–75 ppm) in 1960 and 2.4 ppm (range 0.6–5.0 ppm) in 2002 (Table 2). The median of T-Hg concentrations in hairs of Kitaura cases was 2.8 ppm (range 0.9–9.2 ppm) in 2003 (Table 2). At the same time, it is reported that the geometric mean of T-Hg level in hairs of Japanese was 1.82 ppm from 1999 to 2002 [57]. The residents of Goshoura may not have been exposed to anthropogenic MeHg in the last three decades. Therefore, it implies that their persistent somatosensory disorder is caused by the past 20-year intoxication (1950–1968).

It is known that the axon or the Schwann cells are injured in the peripheral neuropathy. In either case, the distal part of peripheral nerves is selectively damaged [40]. In this report, the quantifiable examinations clarified that the modality of the touch was preserved but the touch thresholds increased

at all body regions in Goshoura subjects and MD patients (Figs. 3 and 5). They did not show the somatosensory reduction at the distal extremities, in the pattern of the so-called “stocking–glove distribution”, which is a characteristic feature of the peripheral neuropathy. These suggest that paresthesia in residents of Goshoura and MD patients is not caused by injuries to peripheral nerves.

Peripheral neuropathy is one of the most common reaction of the nervous system to toxic chemicals. It is known that loss of tendon reflex is common clinical feature in patients with acrylamide or vincristine-induced peripheral neuropathy [28,39]. Whereas, brachioradialis reflex and/or Achilles reflex was often preserved in Goshoura cases, who complained of paresthesia at the distal extremities. Also, in earlier-seen MD patients, tendon reflexes were normal or hyperactive in most of cases, and areflexia was never seen [42]. From these facts, it is unlikely that the somatosensory disorder in Goshoura and MD patients was caused by peripheral neuropathy. When the muscle spindle in the tendon is properly stretched by percussion of a hammer, the nerve impulses enter the dorsal root of the spinal cord and reach an anterior motor neuron. An appropriate reflex signals cause the contraction of the same muscle containing the muscle spindle [17]. If the dorsal ganglions or large myelinated nerves were damaged by MeHg, tendon reflex would be usually lost. The existence of tendon reflex indicates that myelinated peripheral nerves including nerves of touch are intact.

The semilunar ganglion of the trigeminal nerve is said to be analogous to the dorsal ganglion of the spinal nerves. Damage to the bilateral semilunar ganglions is expected to cause the somatosensory disorder in the whole face [32]. However, residents of Goshoura and MD patients complained of the perioral somatosensory disorder, but not in the whole face. Moreover, it is known that damage to central nervous system in the trigeminal nerves causes the somatosensory disorder at the perioral–nasal region as “onion peel” somatosensory distribution [32]. Therefore, it is supposed that the perioral sensory disturbance in Goshoura cases and MD patients is caused by damage to the central nervous system but not to peripheral nervous system including the semilunar ganglion.

As shown in the following studies, somatosensory disturbances were still detected in MD patients more than

Table 2
T-Hg concentrations in hairs of Goshoura and Kitaura subjects

Village (year)	Median ppm	IQR ppm	No. of cases	Minimum ppm	Maximum ppm
Goshoura (1960)	37.0	39.9	16	10.0	75.0
Goshoura (2002)	2.4	1.5	23	0.6	5.0
Kitaura (1960)			Not examined.		
Kitaura (2002)	2.8	2.4	25	0.9	9.2

In 16 cases among 32 Goshoura subjects examined, the hair T-Hg values in 1960 were found to be measured by Doi and Matsushima [11]. T-Hg concentrations in hairs of Goshoura and Kitaura cases in 2002 were measured by our group. The geometric mean of T-Hg level in hairs of Japanese was 1.82 ppm from 1999 to 2002 [57].

10 years after the cessation of exposure to MeHg [34,45]. Nagaki et al. conducted electrophysiological and histopathological examinations in the sural nerves of 8 MD patients, who had persistent disturbances. Their results clarified that the peripheral nerves were not injured in MD patients [34]. Furthermore, Tokuomi et al. studied the persistent disorders in MD patients by examining SSEP and clarified that those were caused by damage to the somatosensory cortex, but neither the peripheral nerves nor the spinal cord nor the thalamus [45]. These results confirm that the lesion of the persistent somatosensory disturbances in MD patients is in the cerebral cortex, but not in the peripheral nerves.

It is known that the somatosensory cortex acts to analyse and synthesize the individual varieties of somatic sensation [12,47]. Damage to the somatosensory cortex causes disorders of perceptual and discriminative functions rather than the simple appreciation of the stimulation of primary sensory endings. Tactile identification of different shapes (stereognosis), recognition of numbers traced on the skin (graphesthesia), localization of stimuli on the skin, and two-point discrimination are all considered to be cortical sensory function [6,10,15,47]. So as to evaluate the cortical sensory function of people in Goshoura and MD patients, we examined the thresholds of the two-point discrimination. In the somatosensory cortex, some areas of the body are represented by large areas. The cortical areas representing the thumb, forefinger and lip are disproportionately large [8,17,24,30]. Such areas are the most sensitive in the body. So we surmised that the examination of the two-point discrimination at such areas could sensitively detect damage to the somatosensory cortex.

Considering the fact that the thresholds of two-point discrimination increase with age [29,41], we examined the control group whose age was comparable to that of Goshoura cases. According to D.S. Louis et al. and J.C. Stevens, the threshold of two-point discrimination in the forefinger of 70 year-old people is about 4 mm [29,41]. This value is almost comparable to that of the control group (Fig. 4). The mean values of the thresholds of Goshoura cases were about two times higher than that in the control group (Fig. 4). The increases of the thresholds in MD patients were comparable to those in Goshoura subjects (Table 1, Fig. 4). In addition, the increases of the thresholds of the two-point discrimination in the thumbs and the tip of tongue of MD patients were observed (Table 1). The disorders of two-point discrimination were frequently detected in MD patients as well as the cases reported by Hunter et al. and Iraqi cases reported by H. Rustam and T. Hamdi [21,38,42]. The extent of damage to the somatosensory cortex in Goshoura cases would be comparable to that in MD patients because values of the thresholds of touch and two-point discrimination in Goshoura subjects were as high as those in MD patients. Taken together, we may logically suppose that the past damages to the somatosensory cortex would cause the

persistent somatosensory disorders in all cases of MeHg poisoning.

Besides, the apraxia limb kinetics, astereognosis and disorder of active sensation, which are all associated with damage to the somatosensory cortex [6,12], were often detected in residents of Goshoura and MD patients. Specifically, they were unskillful in fastening buttons and tying the strings. They also had difficulty in distinguishing a triangular pencil and a hexagonal pencil. These phenomena were not generally observed in the control group. These results are consistent with our idea that MeHg poisoning causes the persistent somatosensory disorders which is due to damage to the somatosensory cortex.

The somatosensory cortex in post-central gyrus is known as the granular cortex containing dense numbers of granule cells [48]. Since it has been proven that small neurons in the central nervous system are most vulnerable to MeHg [4], it is inferred that the diffuse decrease of granular cells in the somatosensory cortex causes the deficiency phenomena in the somatosensory cortex.

In most of patients with parietal disease, it is said that the sensory disturbances cannot be regarded as the manifestations of a purely cortical defect, and the patient is ordinarily not aware of a deficit [10]. Residents of Goshoura and MD patients have not been aware of the sensory disturbances in their whole body. Thus, it is speculated that paresthesia at the distal parts of the extremities is a subjective complaint of MeHg poisoning patients. The crude clinical tests using a painting brush and pinprick are effective in evaluating gross sensory response. However, they are not quantifiable and their reproducibility is poor [5,31]. On the other hand, the examinations of threshold of touch and two-point discrimination are semiquantitative, and more reproducible and reliable than the crude clinical tests [3,31,40]. Consequently, it could be stated that the quantifiable sensory examinations are more suited to detect the somatosensory disorders caused by damage to the cerebral cortex. Provided that the tester is always dependent on the reply from the subject during the examination, these quantifiable tests are not absolutely objective.

It should be noted that aging causes the increase of the thresholds of two-point discrimination [29,41]. Owing to the fact that the values of thresholds of the control group were higher than those of younger people [50] and almost comparable to those of normal old people [29,41], it is suggested that the quantifiable somatosensory examinations of age-matched control people are prerequisite for evaluations of old patients.

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