ELSEVIER

Journal of the Neurological Sciences 262 (2007) 131–144

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

Minamata disease revisited: An update on the acute and chronic manifestations of methyl mercury poisoning

Shigeo Ekino [a,*], Mari Susa [b], Tadashi Ninomiya [a], Keiko Imamura [a], Toshinori Kitamura [c]

[a] Department of Histology, Graduate School of Medical Sciences, Kumamoto University, Honjo, 860-8556 Kumamoto, Japan
[b] Faculty of Law, Kumamoto University, Kurokami, 860-8555 Kumamoto, Japan
[c] Department of Psychological Medicine, Graduate School of Medical Sciences, Kumamoto University, Honjo, 860-8556 Kumamoto, Japan

Available online 2 August 2007

Abstract

The first well-documented outbreak of acute methyl mercury (MeHg) poisoning by consumption of contaminated fish occurred in Minamata, Japan, in 1953. The clinical picture was officially recognized and called Minamata disease (MD) in 1956. However, 50 years later there are still arguments about the definition of MD in terms of clinical symptoms and extent of lesions. We provide a historical review of this epidemic and an update of the problem of MeHg toxicity. Since MeHg dispersed from Minamata to the Shiranui Sea, residents living around the sea were exposed to low-dose MeHg through fish consumption for about 20 years (at least from 1950 to 1968). These patients with chronic MeHg poisoning continue to complain of distal paresthesias of the extremities and the lips even 30 years after cessation of exposure to MeHg. Based on findings in these patients the symptoms and lesions in MeHg poisoning are reappraised. The persisting somatosensory disorders after discontinuation of exposure to MeHg were induced by diffuse damage to the somatosensory cortex, but not by damage to the peripheral nervous system, as previously believed.

Keywords: Methyl mercury poisoning; Somatosensory disorders; Minamata disease; Cortical damage

1. Introduction

In the early 1950s, massive methyl mercury (MeHg) poisoning of residents living around Minamata Bay, a small inlet located on the southwestern coast of Kyushu island, Japan, (Fig. 1) first raised awareness of the resulting severe neurological disease [33]. Since the victims lived near the Bay, this neurological disorder was named Minamata disease (MD). The primary route of exposure to MeHg in this incident was the consumption of fish and shellfish contaminated with a high concentration of MeHg [33]. MeHg chloride, which was produced as a by-product in the acetaldehyde plant of the chemical factory located there, was detected in the wastewater from the acetaldehyde plant, but not from its vinyl chloride plant [12,13]. Initially, this contaminant had been released into Minamata Bay for more than a decade [13] causing severe acute poisoning cases in the vicinity [33]. Acetaldehyde is an intermediate by-product in the manufacture of plastics and its production had expanded steadily to meet the growing demands for plastics at that time. In order to increase production, the factory had expanded the manufacturing plants and changed the drainage site from Minamata Bay to the mouth of the Minamata River [18,24]. This resulted in further dissemination of the pollution into the surrounding waters of the Shiranui Sea (Fig. 2A). The factory continued the production of acetaldehyde and the release of MeHg into the sea waters until 1968 [40,47]. Because fishing in that part of the Shiranui Sea was never restricted, people living in coastal areas–many of whom depended on the sea for a large part of their food supply–were exposed to MeHg by ingestion of polluted fish for almost 20 years [24,25] resulting in chronic MeHg poisoning.

In this article, the clinical symptoms of the acute poisoning cases are first reviewed. Neurological effects in adult cases and fetal cases are discussed separately. Secondly, we discuss

* Corresponding author. Tel.: +81 96 373 5044; fax: +81 96 373 5048.
E-mail address: ekino@gpo.kumamoto-u.ac.jp (S. Ekino).

0022-510X/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.jns.2007.06.036

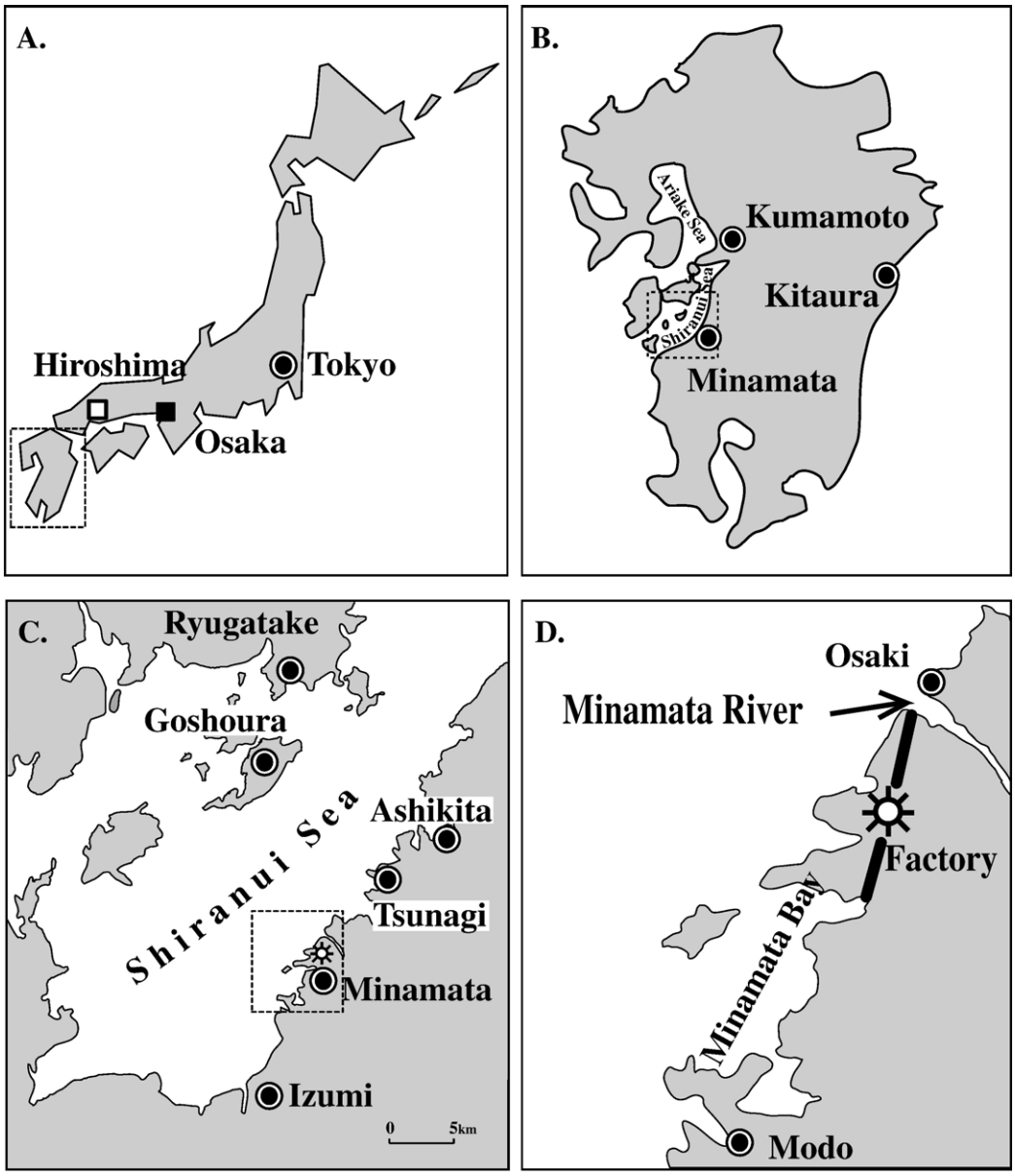


Fig. 1. The map of Japan (A), Kyushu Island (B), Shiranui Sea (C), and Minamata Bay (D). Minamata is located on the coast of the Shiranui Sea in the Kyushu Island, the southern part of Japan (A, B, C). The factory in Minamata discharged MeHg into Minamata Bay and Minamata River (D). Two bold lines indicate two different channels to discharge wastewater from the plant (D). The surface area of Minamata Bay and the Shiranui Sea was about 2 km^2 and 1200 km^2, respectively [25].

the features of chronic MeHg poisoning and the neurological sequelae observed in the population with continued MeHg exposure, after the acute exposure in former years had apparently ceased.

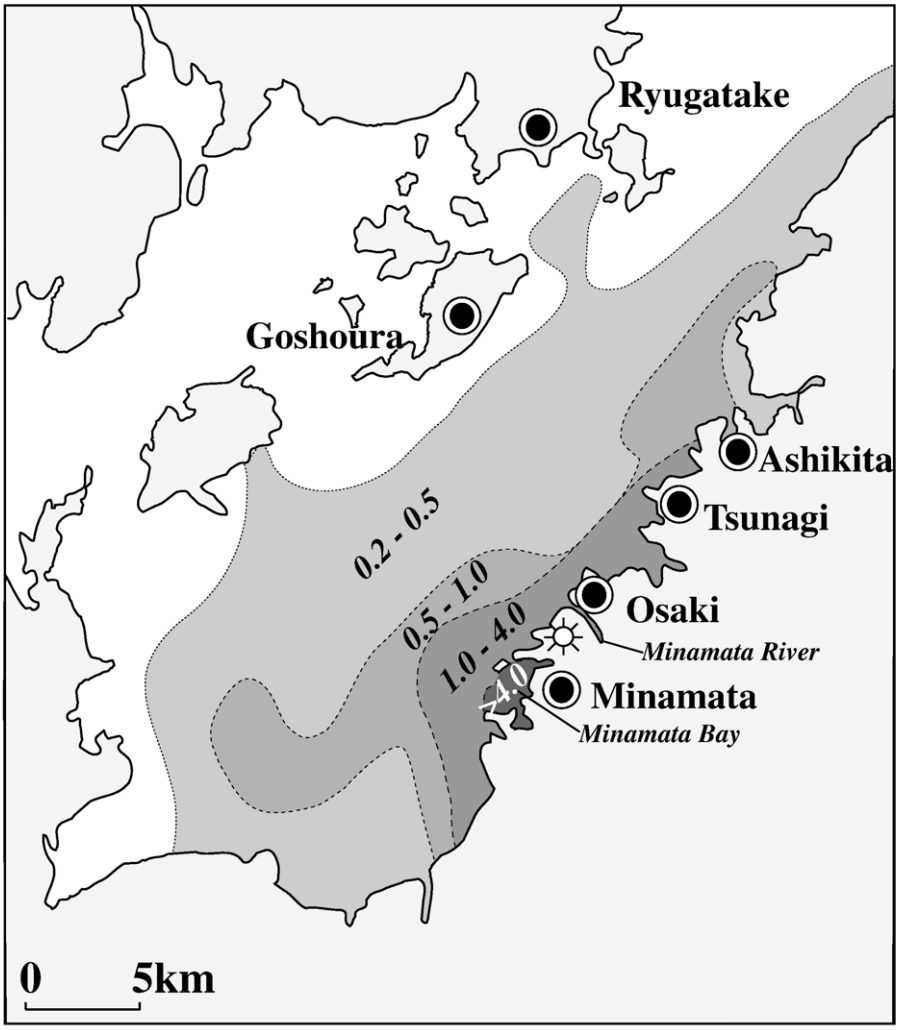
2. Incidence in local residents

Since the initial outbreak of MD in 1953, the number of affected patients has reached 2264 as of the year 2000 [20].

Fig. 2. Expansion of anthropogenic MeHg pollution from Minamata. Mercury levels in the sediments of the Shiranui Sea in 1996 (A). It is ranging from the highest value of 4 ppm at the sampling point at Minamata Bay to the low value of 0.2 ppm at outer points in the Shiranui Sea [40]. The sedimentary sludge containing more than 25 ppm of T-Hg had been dredged since 1980, and it was completed as the sludge was landfilled in 1987. The highest level of T-Hg in Minamata bay was 553 ppm before dredging began, and it fell to 12 ppm with an average of 4.65 ppm after the completion of dredging in 1987 [20]. The background level of T-Hg in the sediments of the Shiranui Sea in general is 0.1–0.2 ppm [17]. T-Hg concentrations in hairs of the residents on the coast of Shiranui Seain 1960 (B). This table is taken from Ref. [25]. The local government of Kumamoto Prefecture investigated T-Hg levels in hairs of 1644 residents in 1960 [6]. We summarized the individual data of T-Hg values in their hairs (D). Median and interquartile range (IQR) were calculated. N.D.: none detected.

Nonetheless, it is estimated that there are at least 200,000 suspected cases of MeHg poisoning since the coastal areas around the Shiranui Sea had a population of about 200,000 in 1960 [20,25]. In Japan, the terms MD and MeHg poisoning, are used in different ways. Although MD certainly is a form of MeHg poisoning, to be diagnosed as suffering from MD, patients affected by MeHg are required to come forward to be officially recognized. Once they are certified as MD patients, they would be eligible for receiving unabridged compensation. The Diagnostic Guidelines for MD were set up for the

A. Distribution of anthropogenic Hg



B. Total hair Hg of residents in 1960

Village	Median	IQR	No. of cases	Mini.	Max.
	ppm	ppm		ppm	ppm
Minamata	30.0	39.8	199	N.D.	172
Tsunagi	33.0	35.8	101	1.0	191
Ashikita	48.6	33.7	40	1.5	192
Goshoura	21.5	24.0	1160	N.D.	920
Ryugatake	17.5	19.3	87	0.5	167
Kumamoto	2.1	1.3	16	0.1	8

compensation scheme under the Law Concerning Special Measures for the Relief of Pollution-related Health Damage, which was put into effect in 1969 [20]. So far, only about 17,000 of the residents had applied for the certification but only the above-mentioned 2264 were officially authorized.

3. Clinical features

Methyl mercury poisoning observed in the areas around Minamata Bay and then on the coast of the Shiranui Sea is classified into two types: acute and chronic poisoning. As mentioned above, MD is a certified MeHg poisoning according to the Diagnostic Guidelines [36]. This was caused by consumption of polluted fish containing high levels of MeHg in Minamata Bay around 1953. Such severe acute cases had not been found since about 1960, because the residents stopped consuming highly contaminated fish as a result of the boycott in 1959 by the Minamata Bay fishmongers association to all fish and shellfish caught by the Minamata Fishermen's Cooperative. After the factory changed its effluent outlet in 1958 from Minamata Bay to the mouth of Minamata River [18,47], the anthropogenic MeHg contamination was dispersed to the Shiranui Sea. Because a ban on commercial fishing was never placed in this sea, chronic MeHg poisoning resulted from ingestion of contaminated fish from the Shiranui Sea during almost 20 years (1950–1968). The median value of total mercury (T-Hg) in hair samples of 1644 residents of the coastal areas was 23.4 ppm (range 0–920 ppm) in 1960 [25].

3.1. Acute MeHg poisoning

Acute adult cases of MeHg poisoning [33] present the following manifestations: blurred vision, hearing impairment, olfactory and gustatory disturbances, ataxic gait, clumsiness of the hands, dysarthria, and somatosensory and psychiatric disorders. Children born to mothers exposed to MeHg show extensive spongiosis of the cerebral cortex. This became a characteristic feature of fetal MD [33]. Thus, MeHg was recognized as being highly neurotoxic to the human brain, and most especially to the developing brain.

3.1.1. Adult acute MeHg poisoning

3.1.1.1. Visual impairment. A conspicuous feature of the disease is bilateral and symmetric concentric constriction of the visual fields (Fig. 3), observed in all cases [38]. Remarkable variation in constriction of the visual field was often observed [15]. This changeability of the visual field was suspected to be functional, but not organic. In addition, abnormalities of spatial contrast sensitivity and of stereopsis were detected in a high percentage of cases [14]. On the other hand, visual acuity, optic fundi, ocular movements, and pupillary reflexes were normal. Neither anisocoria nor nystagmus was detected [38]. These observations suggest that the visual center of the occipital lobe is strongly affected. These clinical suggestions were supported by pathological studies showing deciduation of neurons and proliferation of microglia in the occipital visual cortex [28].

3.1.1.2. Hearing impairment. Bilateral hearing impairment is present; as shown by the pure-tone audiometry in Fig. 3 [38]. In pure-tone air conduction threshold tests, the threshold was about 20 db at 125–3000 cps (cycles per second). It gradually went down from 3000 cps and showed the lowest values at 5000–8000 cps (Fig. 3). Pure-tone loss in acute MeHg poisoning patients was less severe than in laborers with noise deafness [27]. Speech discrimination was more damaged in comparison with pure-tone loss [11,22]. The acoustic impedance test battery demonstrated few abnormalities of the peripheral auditory mechanism [22]. Pathological studies, as well as clinical findings, indicate that the primary auditory area of the temporal lobe was strongly affected.

3.1.1.3. Olfactory and gustatory disturbances. Patients with acute poisoning often complained of subjective changes in the sense of smell and loss of taste after the first attack of MeHg poisoning [27]. There were increases of the detection threshold and the recognition threshold in smell perception. However, in these patients, few pathological findings related to olfactory disturbances have been observed in the nose and paranasal sinuses by rhinological examination [22]. The gustatory disorder was also detected by means of electric gustometry and/or semi-quantitative tests [22,27]. The olfactory and gustatory disturbances could be considered to originate from cortical lesions because cranial nerves were found to be almost free of alterations in pathological studies [32,34].

3.1.1.4. Cerebellar ataxia. In acute cases, bilateral disturbances of complex movements were remarkably prominent. Dysmetria, adiadochokinesis, alterations of speech, writing problems and gait disturbances were always detected [38]. In detection of dysmetria, the finger-to-nose and heel-to-knee tests were employed. When the finger overshot its goal, hypermetria was seen to be present, or when it failed to reach the goal, hypometria was seen to be present. These abnormalities indicated the disorder of a movement requiring muscle action at two or more joints. Adiadochokinesis was a sign to show a disturbance of the ability to perform rapid alternate movements. It was usually demonstrated by having the patient supinate and pronate the forearms and slap the palms and then the dorsum of the hands on the knees. As the movement gained speed, the disorder became more apparent [7]. At autopsy, the cerebellum showed bilateral diffuse atrophy, and microscopically, there was diffuse loss of granule cells in granular layer of bilateral cerebellar cortices [32,34].

3.1.1.5. Somatosensory disturbances. A primary symptom in these patients was the complaint of various types of distal paresthesias of the extremities and around the lips, including

tingling, numbness, hypesthesia, thermohyperesthesia and hypalgesia [38]. When those patients were examined with conventional sensory tests using a painting brush and pin-prick, the sensory reduction at the distal extremities was detected [38]. These sensory impairments had a tendency to improve. On the other hand, the disturbances of discriminative sensory function such as two-point discrimination and sterognosis remained for a long period [38]. Tendon reflexes were normal or hyperactive in most of cases and areflexia was never seen [38]. This existence of tendon reflex indicates that myelinated peripheral nerves remain intact. Also, damage to the peripheral nervous system was not detected in pathological examinations [34]. From these facts, it is unlikely that the somatosensory disorder in acute MeHg poisoning patients was caused by peripheral neuropathy.

3.1.1.6. Psychiatric symptomatology. Tatetsu reported that he and his colleagues examined 44 adult cases of the disease in 1961 to 1962 and followed 40 of them in 1964 to 1966 and additional four cases in this period [37]. Acute MeHg

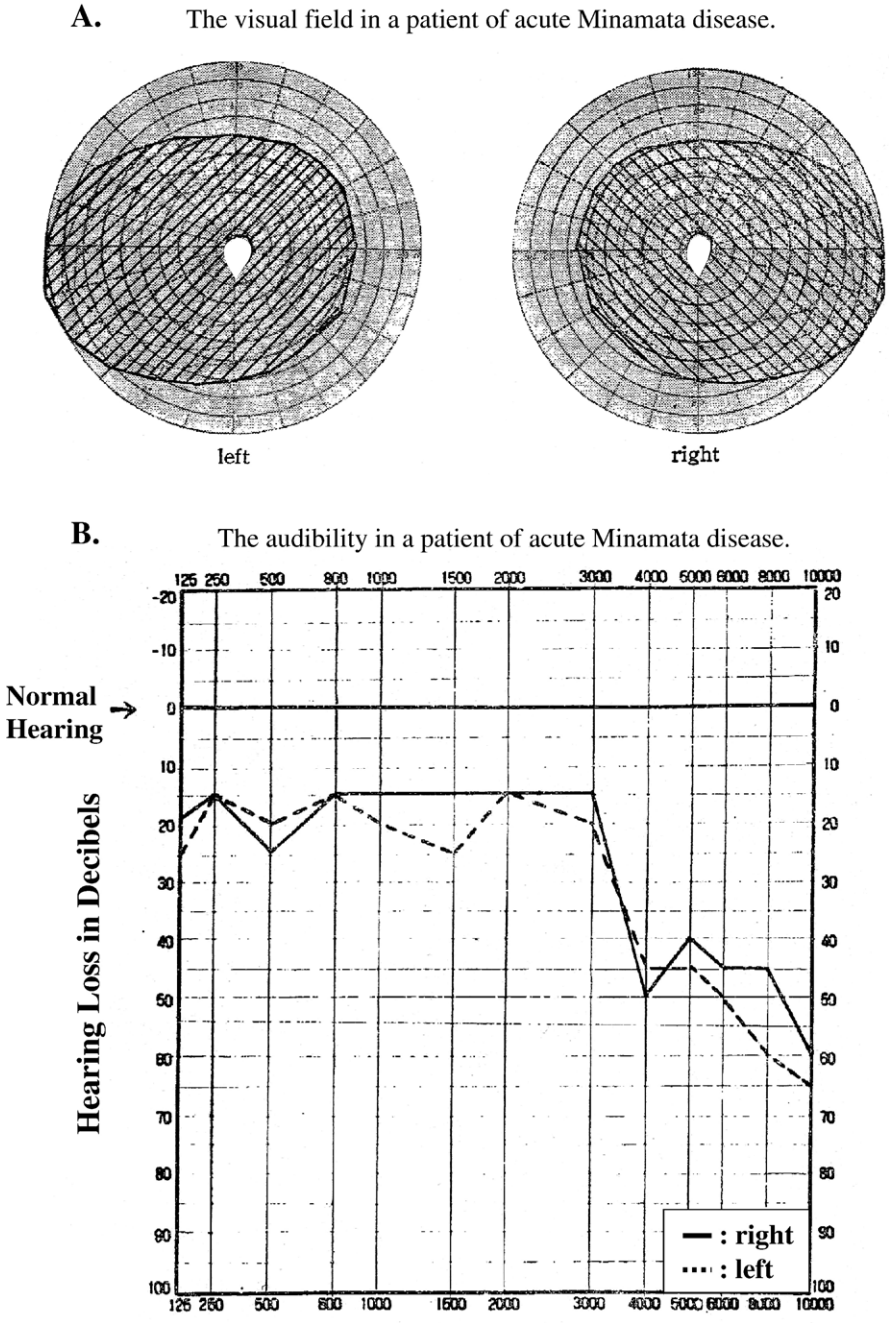


Fig. 3. Concentric constriction of bilateral visual fields (A) and bilateral hearing impairments (B) in a patient of acute Minamata disease in 1956. These figures are taken from Ref. [38].

poisoning cases were categorized into three groups based on neuropsychiatric findings: (1) akinetic mutism or hyperkinesia with severe intellectual and emotional disabilities, (2) ataxia with/without extrapyramidal symptoms or intellectual/personality disabilities, and (3) intellectual/personality disabilities. Tatetsu [37] stressed that all the 1961–1962 and 1964–1966 cases manifested symptoms of personality, emotion, or volition. Most of the cases showed loss of volition/apathy to a varying extent. They were lethargic, became tired easily and were unable to perform a slightly difficult task. They lacked emotional expression and spontaneity. While they showed little interest in the surroundings and had little warmth in expression, they showed occasionally emotional lability. They showed lack of initiative in negotiating with others, talked little, did not carry out their duty chores at school unless prompted, and moved slowly. A second characteristic of these cases was the excessive interpersonal sensitivity. They avoided meeting with others, their contact was superficial, or they did not respond to questioning. They were difficult to approach, little amiable, and showed no interest to others even the family members. While interviewing, their voice was low and they often looked down. Six cases (whose intellectual disability was mild) refused the medical interviewing and ran from the room. A third aspect of their personality was the abnormal perseveration in that they persisted on one thing once they started it. They often did the same thing (e.g., writing, walking in the corridor) repeatedly. They placed vases in a straight line, wrote letters extremely clearly on paper, and took note the number of going to the toilet everyday. They were egocentric, selfish, and paid little attention to the advices of others. Loss of inhibition was another feature of the disease's personality characteristics. They were often impolite, too friendly to others, easily burst into anger, restless, euphoric, and childish. Some of them spent money as much as they were given and threw away change.

3.1.2. Fetal MeHg poisoning

Serious disturbances in mental and motor developments were observed in all cases of fetal MeHg poisoning. They showed significant impairments in chewing, swallowing, speech, gait, other coordination and involuntary movement. These impairments were always bilateral. These symptoms were induced by the diffuse damage to the brain [9,34]. Mental disturbance had a close relation with motor disturbance. M. Harada reported that the symptoms of the congenital cases included (1) psychomotor disturbance and intellectual disability, (2) personality disturbance, (3) epileptic fits, and (4) neurological symptoms. As in the adult cases, the most severe cases were with akinetic mutism. As regards their personality, they were extremely shy, difficult to approach, and ran away when talked to. They took little initiative, less amiable, cold, and showed little facial expression. Some of them were sensitive, easily became angry or violent (e.g., hitting others and throwing things). Some of them were hyperkinetic; they were restless, and attention was distracted. Others startled easily to stimuli such as sound [37].

3.2. Chronic MeHg poisoning

The existence of chronic MeHg poisoning cases on the coast of the Shiranui Sea has not been well-acknowledged until 1995 [24]. These chronic poisoning patients principally have complained of paresthesia at the distal parts of the extremities and around the lip since the cessation of

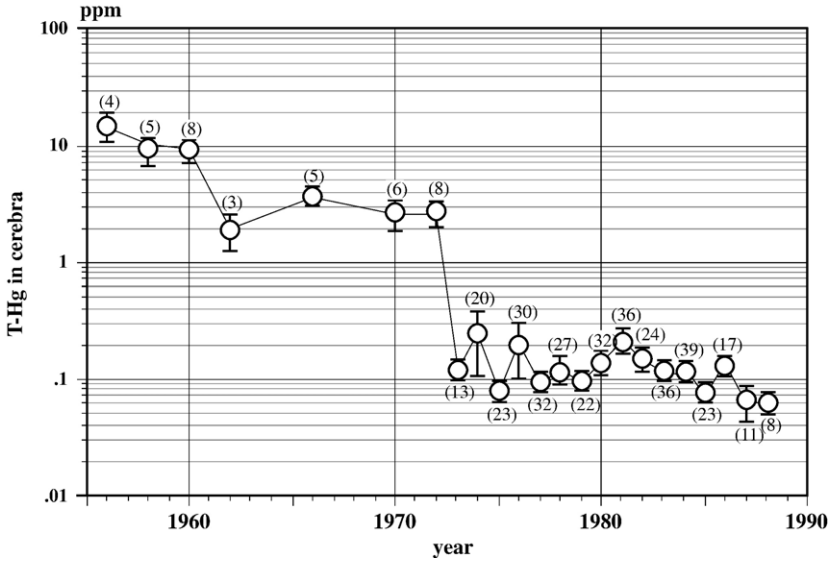


Fig. 4. The trends in levels of T-Hg in cerebra of residents on the coast of the Shiranui Sea from 1956 to 1988. Pathological autopsies of samples from 428 residents who had applied for the certification after suffering from MeHg poisoning. T-Hg concentrations in cerebra of these residents were studied and reported [35]. We added up individual data of 428 samples in each year and made a graph. Each point represents the mean. Vertical bars express the standard error of the mean. Figures in parentheses represent the number of samples examined.

MeHg pollution even though their exposure appeared to be ceased more than 30 years ago. It is reported that, in primate, the concentrations of Hg in brain had decreased dramatically after the termination of exposure [41]. The abrupt decline of the T-Hg levels in the cerebrum of the local residents was shown in Fig. 4. The fact that the T-Hg concentrations reached to the almost normal level in 1973 (Fig. 4), may illustrate that their exposure had ended about that time. The duration of their exposure is considered to be about 20 years (at least from 1950 to 1968) (Fig. 5). Their median value of T-Hg in hairs was 23.4 ppm (range 0–920 ppm) in 1960, when MeHg pollution reached a maximum (Fig. 5A) [25]. Extrapolating from the temporal changes in MeHg concentrations in the umbilical cords (Fig. 5A), the average value of T-Hg in hairs during the 20 years period of pollution would be approximately calculated to be the half of the value in 1960.

3.2.1. Somatosensory disturbances

When chronic poisoning patients 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 [25]. Then it has been believed that this sensory disorder was a symptom caused by damage to peripheral nerves, leading to a diagnosis of the peripheral neuropathy. Yet, tendon reflex of chronic MeHg poisoning cases, who have complained of paresthesia at the distal parts of the extremities, were often preserved [25]. Therefore, it is questioned whether their disorders were caused by injuries to their peripheral nerves. In case of MeHg poisoning in rats, studies clarify that the neurological effects of MeHg is on damage to the peripheral sensory nerves and/or the dorsal root ganglion [46,49]. These observations in rats were conveniently extrapolated to human MD patients without control studies [8,21]. However, definitive scientific data on damage to human peripheral nervous system by MeHg have not been reported [48].

Nagaki et al. performed electrophysiologic and histopathologic studies on sural nerve of MD patients in comparison with control people in 1985 [23]. Maximum conduction velocity (MCV) and the amplitude of the nerve action potential of sural nerve of MD patients and control people were compared. In histopathologic studies, fascicular biopsy specimens of the sural nerve were taken 2 cm above the right lateral malleous. The morphometric evaluation of the densities of myelinated and unmyelinated fibers was performed. Electrophysiological and histopathological results of MD patients were comparable to those of control people (Table 1). The electrophysiological results gotten by Nagaki are consistent with those of MeHg poisoning studied in Iraq [19,30,43]. 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

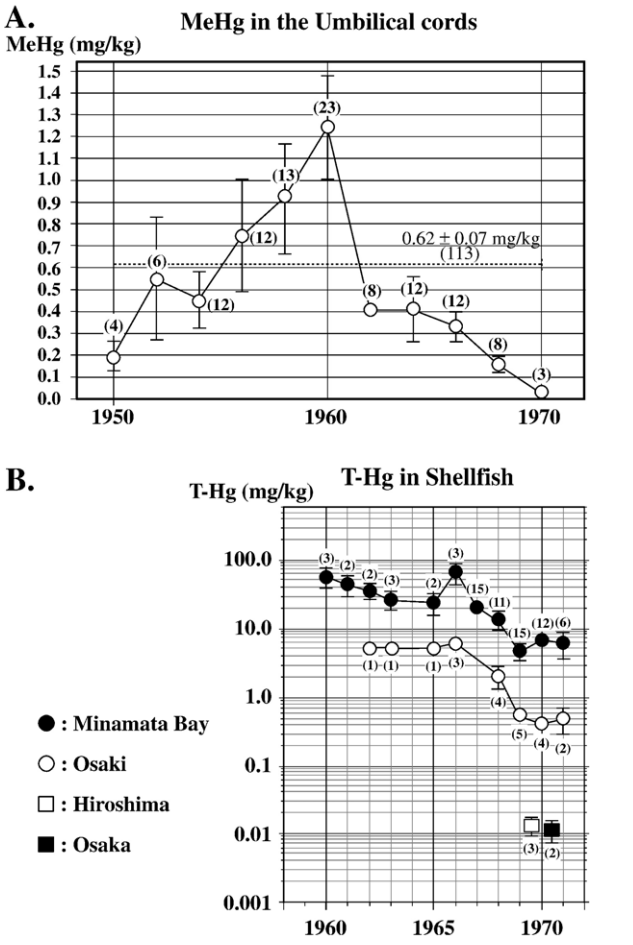


Fig. 5. Duration of mercury pollution caused by Minamata factory. The temporal changes in MeHg concentrations in the umbilical cords of the residents on the coast of the Shiranui Sea from 1950 to 1970 (A). Japanese families have maintained the tradition to keep a small piece of the umbilical cords in memory of the birth. The Hg concentration in the umbilical cord correlates well with that in maternal hair [1]. Therefore, MeHg concentrations in the umbilical cords of the residents would indicate the degree and extent of MeHg pollution. We added up individual data of 113 umbilical cords in every two years from 1950 to 1970 and made a graph. Each point represents the mean. Vertical bars express the standard error of the mean. Figures in parentheses represent the number of samples examined. A broken line indicates the mean value (0.62±0.07 ppm (Mean±SE)). The mean of MeHg concentrations in the umbilical cords of 24 inhabitants of Tokyo was 0.11±0.03 ppm (Mean±SD) in 1975 [26]. The individual data were kindly provided by Dr. M. Harada. Temporal changes in mercury concentrations in shellfish caught at Minamata Bay and at the mouth of Minamata River (Osaki) (B). Individual data from Irukayama's paper were analyzed [13]. Mean value of T-Hg concentrations in shellfish from Hiroshima and Osaka was 0.013±0.04 ppm and 0.011±0.04 ppm (Mean±SE) in 1970, respectively [16]. Each point represents the mean. Vertical bars express the standard error of the mean. Figures in parentheses represent the number of samples examined.

sensory disorder in MD patients is in the somatosensory cortex, but neither the peripheral nerves nor the spinal cord nor the thalamus [39] (Fig. 6). So these results clarified that the lasting somatosensory disturbance in MD patients is not caused by injuries to the peripheral nerves.

Table 1
Electrophysiologic and pathologic studies on sural nerves in Minamata disease (MD)

	Control	MD
Subjects	8	8
Age	58.8±14.3 [a]	59.5±7.8
Electrophysiologic examinations on sural nerves		
MCV (m/s) [b]	50.63±2.63	49.31±4.01
Amplitude (μV) [c]	21.50±15.03	17.38±10.13
Pathologic examinations on sural nerves		
No. of LMF (No./mm) [d]	3257±889	3276±950
No. of SMF (No./mm) [e]	4130±844	4436±1343
No. of UMF (No./mm) [f]	27,866±5820	25,020±8265

These data are taken from Ref. [23].
[a] Mean±SD.
[b] Maximum conduction velocity.
[c] The amplitude of the nerve action potential.
[d] Large myelinated fiber (The diameter of myelinated fibers was more than 5 μm).
[e] Small myelinated fiber (The diameter of myelinated fiber was 5 μm or less).
[f] Unmyelinated fiber.

3.2.1.1. The touch thresholds of chronic MeHg poisoning patients. The modality of touch was preserved in patients. Their touch thresholds increased not only at the distal extremities but also at the proximal extremities and trunks. 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. The laterality was not observed [25], (Fig. 7). In the study of the touch thresholds examined at 13 body regions of each side in certified MD patients, it is revealed that the increases in thresholds were observed in all body regions

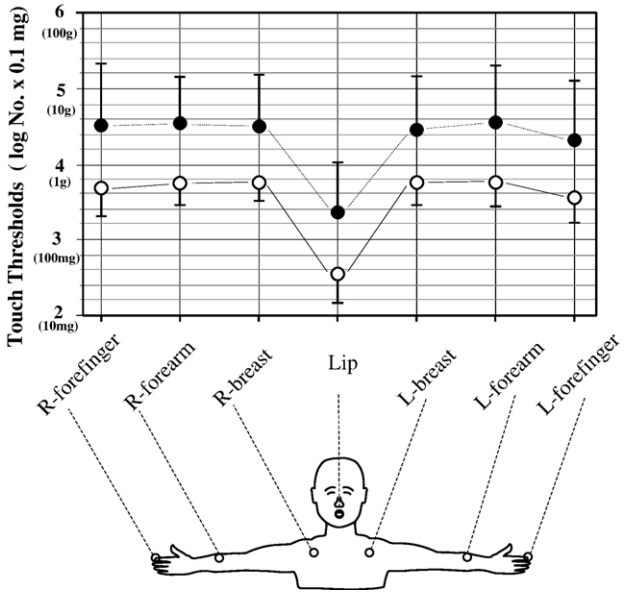


Fig. 7. The thresholds of touch in chronic MeHg poisoning subjects (closed circle) and control subjects (open circle). Forefingers, forearms and breasts of both sides, and the tip of lower lip were examined. Each point represents the mean. Vertical bars express the standard deviation of the mean. These results clarified that touch thresholds of chronic 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. This figure is taken from Ref. [25].

(Fig. 8). These data suggest that the systemic increases of touch thresholds in chronic poisoning patients would be noted.

3.2.1.2. The thresholds of two-point discrimination. Patients could perceive the stimulation of one point and

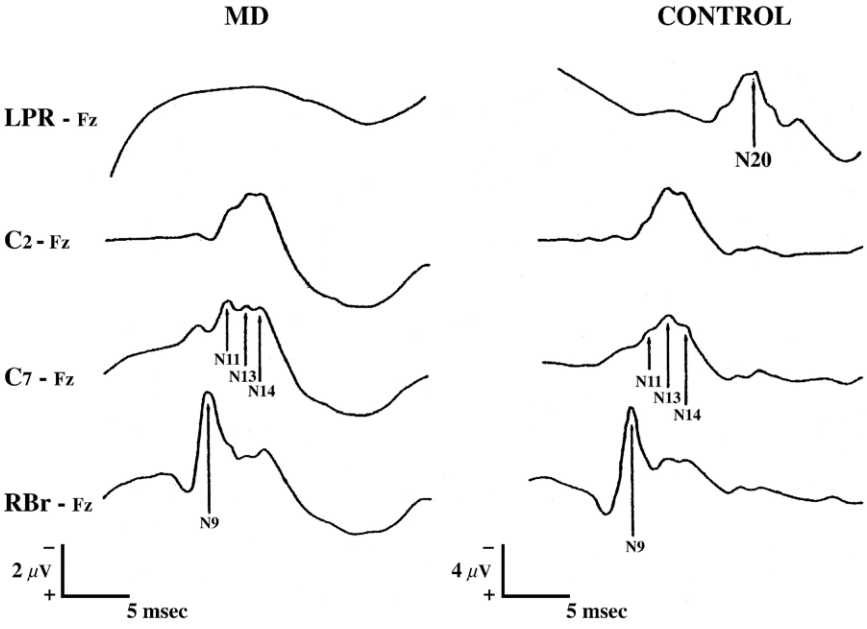


Fig. 6. Short-latency somatosensory evoked potential (SSEP) in a Minamata disease (MD) patient (A) and a normal subject (CONTROL) (B). The N20 component of SSEP was completely absence in Minamata disease. LPR: left postrolandic area, RBr: right brachial plexus. This figure is taken from Ref. [39].

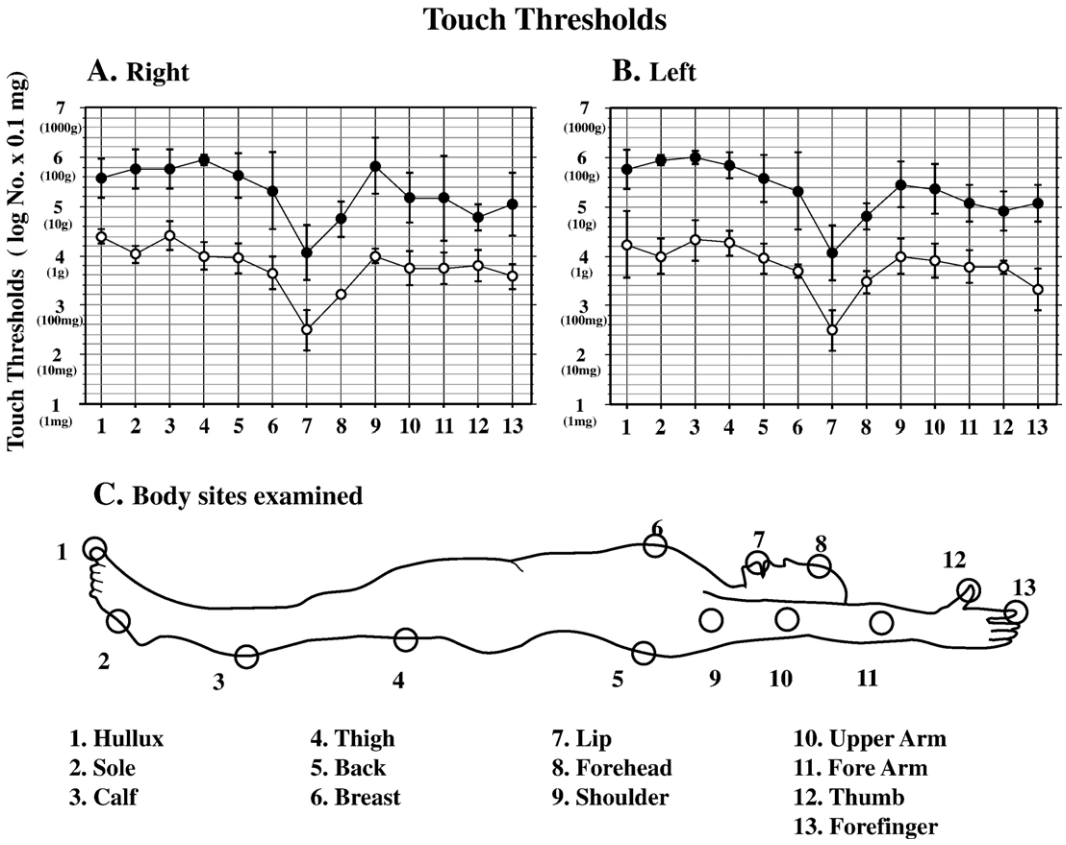


Fig. 8. Touch thresholds in MD patients (closed circle) and control people (open circle) (A: right, B: left). Systemic increases of touch thresholds were observed in MD patients. Touch thresholds were measured with a set of modified von Frey-type filaments [31,45]. Filaments are calibrated to provide 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 10 g of force) [31]. (C) Thirteen body regions were selected according to the report of S. Weinstein [45]. 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. Three MD patients and three control people were studied. Each point represents the mean. Vertical bars express the standard deviation of the mean. The mean mercury concentration in the hair of MD patients studied was 54.0±7.9 mg/kg in 1960.

recognize the duality of two points even at a small distance when two points are applied successively. When the thresholds of two-point discrimination at the tongue, the lip, the forefingers and the thumbs of the patients were tested, the results were shown to be about two times as high as those of the control people, showing comparable results obtained in the study on the MD patients [25] (Fig. 9). The two-point discrimination is known to be associated with the function of the somatosensory cortex [3,42]. Therefore, it is proposed that the persisting somatosensory disorders of chronic MeHg poisoning patients are induced by diffuse damage to the somatosensory cortex, but not the peripheral nerves. In the somatosensory cortex, the portions representing the tongue, the lip, the forefinger and the thumb occupy disproportionately large areas [4,29] (Fig. 10). Then, it is surmised that chronic MeHg poisoning causes diffuse damages to the bilateral somatosensory cortices and the persistent somatosensory disturbances in patients [25].

It is known that the somatosensory cortex acts to analyze and synthesize the individual varieties of somatic sensation [5,42]. Damage to the somatosensory cortex causes disorders of perceptual and discriminative functions rather than the simple appreciation of the stimulation of primary sensory endings. This explains the fact that the apraxia limb kinetics, astereognosis and disorder of active sensation, which are all associated with damage to the somatosensory cortex [3,5], were often detected in the patients. Unskillfulness in fastening buttons and tying the strings was also observed in them [25].

3.2.2. Other symptoms

MeHg intoxication causes damage to the layer of granule cells in cerebellum and hence cerebellar ataxia [33]. Cerebellar ataxia was observed in the patients and had a tendency to improve after the cessation of exposure [10]. Therefore, this cerebellar ataxia is difficult to observe 30 years after the exposure. On the other hand, damage to the somatosensory cortex causes the impairment of postural sense. This may result in sensory ataxia and pseudoathetoid movements. This sensory ataxia is often detected even now [25].

Damage to the primary visual area of the occipital lobe and the primary auditory area of the temporal lobe were also reported in acute poisoning cases [33]. In the preliminary studies by Ninomiya et al., the disorders of visual and

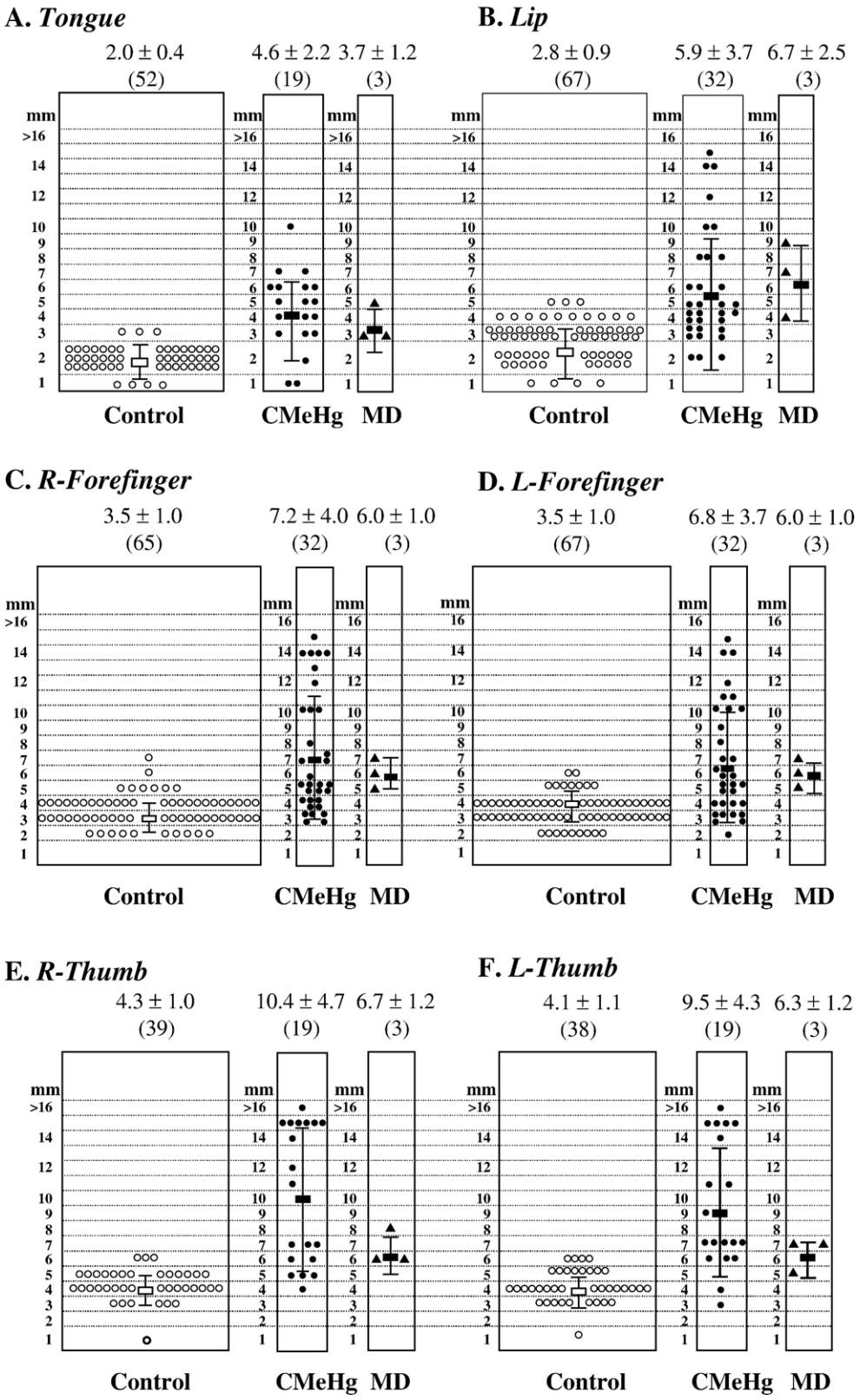


Fig. 9. The thresholds of two-point discrimination in control (open circle), chronic MeHg poisoning (closed circle), and Minamata disease (triangle) subjects. Lip (A), lower lip (B), right forefinger (C), left forefinger (D), right thumb (E) and left thumb (F) were examined. Each point represents the threshold of two-point discrimination in the individual subjects examined. The mean is indicated by a rectangle. Vertical bars express SD of the mean. *Mean ± SD (the number of subjects examined). The thresholds of two-point discrimination in chronic MeHg poisoning subjects (CMeHg) were about two times as high as those of the control subjects, and comparable to or rather higher than those of MD subjects.

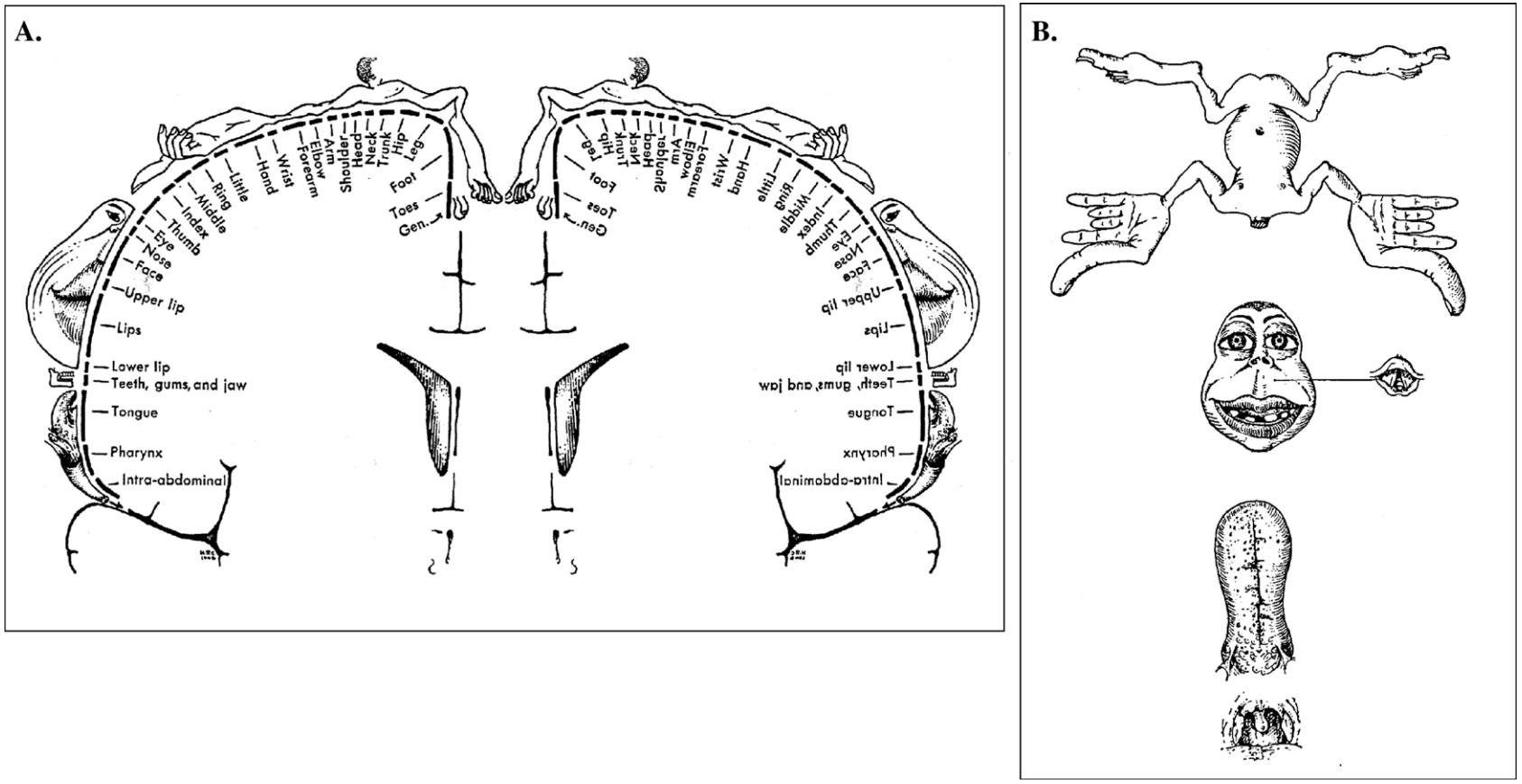


Fig. 10. Sensory homunculus (A). Representation of examined body regions in the somatosensory cortex. Areas of the body that are important for tactile discrimination, such as the tip of the tongue, the lip, the thumb and the forefinger, have a disproportionately larger representation, reflecting their more extensive innervation [4,29]. Sensory and motor homunculus (B). This was prepared as a visualization of the order and comparative size of the parts of the body as the body as they appear from above down upon the Rolandic cortex. These figures are taken from Ref. [29].

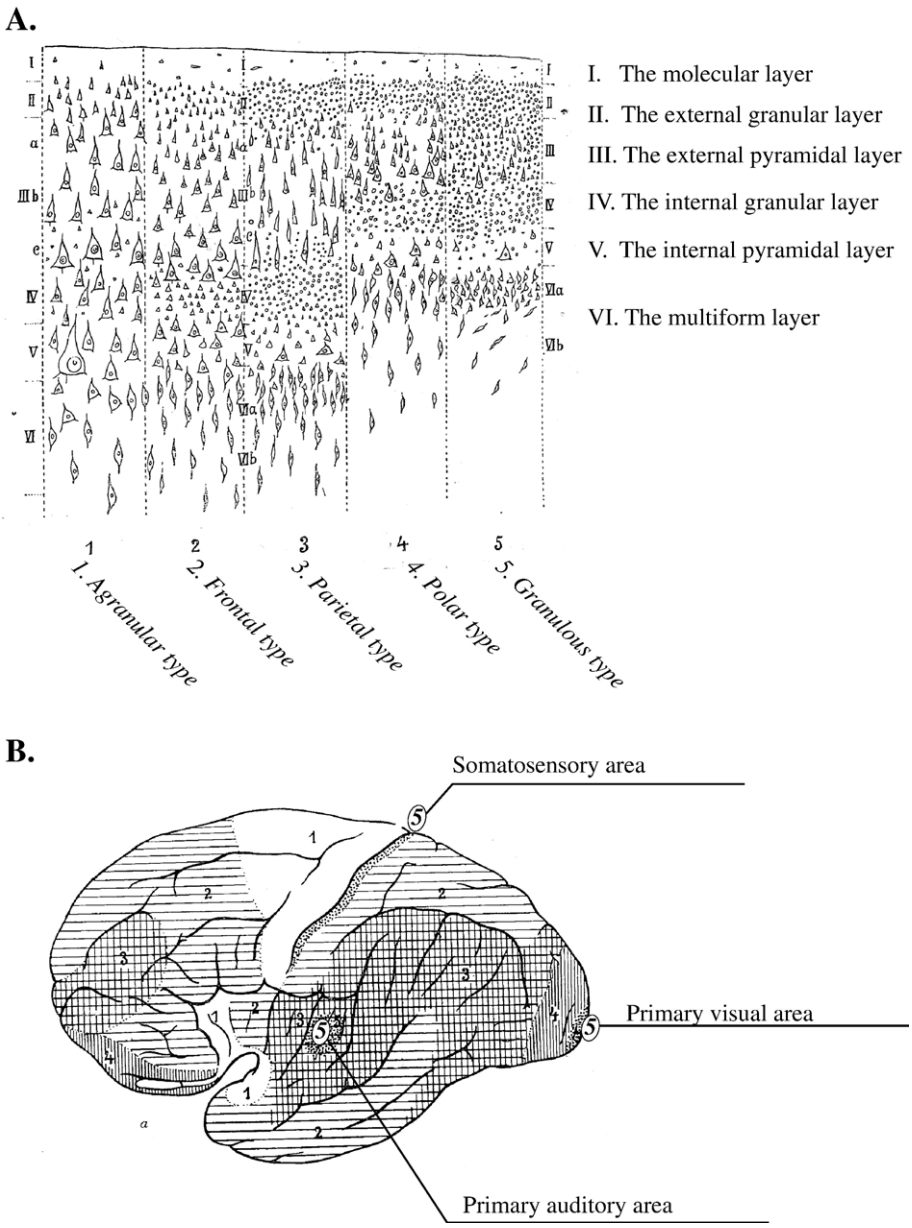


Fig. 11. The five fundamental types of the neocortex (A). In sections stained by Nissl method, cell bodies are not uniformly distributed. Each layer is distinguished by the types, density and arrangements of its cells. In the neocortex, the following layers are distinguished in passing from the pial surface to the underlying white matter: I, molecular; II, external granular; III, external pyramidal; IV, internal granular; V, internal pyramidal; and VI, multiform [44]. Distribution of the five fundamental types of cortex (B). According to von Economo, the structure of the neocortex is reducible to five fundamental types, based primarily on the relative development of granule and pyramidal cells [44]. The granulous type of cortex is extremely thin and is composed mainly of densely packed granule cells. The granulous type of cortex may be regarded as primarily sensory in character, since it is found only in the areas receiving the specific sensory thalamocortical projections. These figures are taken from Ref. [44].

hearing discrimination were observed in chronic poisoning patients.

The somatosensory cortex in human is known as the granulous type of cortex containing dense numbers of granule cells as in the visual and auditory cortex [44] (Fig. 11). The granulous type of cortex is regarded as primarily sensory in character, since it is found only in the areas receiving the specific sensory thalamocortical projections. Since it has been proven that small neurons in the central nervous system are most vulnerable to MeHg [2], it is inferred that the diffuse diminution of granule cells in the cerebral cortex causes the deficiency phenomena in the somatosensory, visual, auditory, gustatory and olfactory system. Further studies are required to clarify the dysfunction of visual and hearing discrimination as well as the disorder of taste and smell in MeHg poisoning.

Acknowledgments

This work was supported by Kumamoto University Library. By the courtesy of Dr. J. Nagaki and Dr. H. Tokuomi,

we were permitted to use data and figures in this article. We thank them for their cooperation. We are grateful to Dr. S. Kawamura for his encouragement.

References

[1] Akagi H, Grandjean P, Takizawa Y, Weihe P. Methylmercury dose estimation from umbilical cord concentrations in patients with Minamata disease. Environ Res 1998;77:98–103.
[2] Berlin M. Mercury. In: Friberg L, Nordberg GF, Vouk V, editors. Handbook on the toxicology of metals. second edition. Flolida: Elsevier; 1987. p. 387–445.
[3] Botez ML, Botez T, Olivier M. Parietal lobe syndromes. In: Frederiks JAM, editor. Handbook of clinical neurology, clinical neuropsychology, vol. 1 (45). Amsterdam: Science Publisher B.V. Elsevier; 1985. p. 63–85.
[4] Carpenter MB. Human neuroanatomy. 7th edition. Baltimore: The Williams Wilkins Company; 1976.
[5] Dejong RN. Sensation. In: Vinken PJ, Bruyn GW, editors. Handbook of clinical neurology, disturbances of nervous function, vol. 1. Amsterdam: North-Holland Publishing Company; 1969. p. 80–113.
[6] Doi S, Matsushima G. The second report on hair mercury concentration in Minamata disease. Kumamoto: Kumamoto Prefectural Institute of Public Health; 1962.
[7] Dow RS. Cerebellar syndromes. In: Vinken PJ, Bruyn GW, editors. Handbook of clinical neurology, Vol. 2: localization in clinical neurology. Amsterdam: North-Holland Publishing Company; 1969. p. 392–431.
[8] Eto K, Takeuchi T. Pathological changes of human sural nerves in Minamata disease (methylmercury poisoning). Light and electron microscopic studies. Virchows Arch B Pathol 1977;23:109–28.
[9] Harada Y. Congenital (or Fetal) Minamata Disease. In: Study Group of Minamata Disease, editor. Minamata Disease. Kumamoto: Kumamoto University, 1968: 93–117.
[10] Hunter D, Bosmford RR, Russell DS. Poisoning by methylmercury compounds. Q J Med 1940;9:193–213.
[11] Ino H, Mizukoshi K. Otorhinolaryngological findings in intoxication by organomercury compounds. In: Tsubaki T, Irukayama K, editors. Minamata disease methylmercury poisoning in Minamata and Niigata, Japan. Tokyo: Kodanasha Ltd; 1977. p. 186–208.
[12] Irukayama K, Tajima S, Fujiki M. Studies on the origin of causative agent of Minamata disease report VIII. On the formation of methyl mercury compounds in an acetaldehyde plant. Methylmercury compounds formed from the reaction of acetaldehyde and inorganic mercury compounds. Jpn J Hyg 1967;22:392–400 [Japanese].
[13] Irukayama K, Ushikusa S, Tajima S, Nakamura H, Kuwahara S, Omori A, et al. Studies on the origin of causative agent of Minamata disease. Report IX. Transition of the pollution of Minamata Bay and its neighborhood. Jpn J Hyg 1967;22:416–23 [Japanese].
[14] Iwata K. Neuro-ophthalmological findings and a follow-up Study in the Agano Area, Niigata prefecture. In: Tsubaki T, Irukayama K, editors. Minamata disease methylmercury poisoning in Minamata and Niigata, Japan. Tokyo: Kodanasha Ltd; 1977. p. 166–85.
[15] Iwata K, Kato I. Neuroophthalmological and pathological studies of organic mercury poisoning. In: Tsubaki T, Takahashi H, editors. Recent advances in Minamata disease studies. Tokyo: Kodanasha Ltd; 1986. p. 58–74.
[16] Japanese Association of Public Health. Environmental pollution by mercury in Japan. Environ Health Rep 1973;23:200 [Japanese].
[17] Kudo A. Natural and artificial mercury decontamination — Ottawa River and Minamata Bay (Yatsushiro Sea). Water Sci Tech 1992;26: 217–26.
[18] Kurland LT, Faro SN, Siedler H. Minamata disease. The outbreak of a neurologic disorder in Minamata, Japan, and its relationship to the ingestion of seafood contaminated by mercuric compounds. World Neurol 1960;1:370–91.
[19] Le Quesne PM, Damluji SF, Rustam H. Electrophysiological studies of peripheral nerves in patients with organic mercury poisoning. J Neurol Neurosurg Psychiatry 1974;37:333–9.
[20] Minamata Disease Municipal Museum. Minamata disease–its history and lessons–2000. Minamata: Minamata City Planning Division; 2000.
[21] Miyakawa T, Murayama E, Sumiyoshi S, Deshimaru M, Fujimoto T, Hattori E, et al. Late changes in human sural nerves in Minamata disease and in nerves of rats with experimental organic poisoning. Acta Neuropathol (Berl) 1976;35:131–8.
[22] Mizukoshi K, Watanabe Y, Kato I. Otorhinolaryngological findings. In: Tsubaki T, Takahashi H, editors. Recent advances in Minamata disease studies. Tokyo: Kodanasha Ltd; 1986. p. 74–115.
[23] Nagaki J, Ohnishi A, Kuroiwa Y. Electrophysiologic and histopathologic studies on sural nerves from Minamata disease patients of delayed onset showing distal sensory impairments. Clin Neurol 1985;25:88–94 [Japanese].
[24] Ninomiya T, Ohomori H, Hashimoto K, Tsuruta K, Ekino S. Expansion of methylmercury poisoning outside of Minamata: an epidemiological study on chronic methylmercury poisoning outside of Minamata. Environ Res 1995;70:47–50.
[25] Ninomiya T, Imamura K, Kuwahata M, Kindaichi M, Susa M, Ekino S. Reappraisal of somatosensory disorders in methylmercury poisoning. Neurotoxicol Teratol 2005;27:643–53.
[26] Nishigaki S, Harada M. Methylmercury and selenium in umbilical cords of inhabitants of the Minamata area. Nature 1975;258:324–5.
[27] Nosaka Y. Impairments in Hearing Acuity, Vestibular Function, Sense of Smell and Taste in Minamata Disease. In: Study Group of Minamata Disease, editor. Minamata Disease. Kumamoto: Kumamoto University, 1968: 119–126.
[28] Oyake Y, Tanaka M, Kubo H, Chichibu M. Neuropathological studies on organic mercury intoxication with special reference to distribution of mercury granules. Adv Neurol Sci (Shinkei Kenkyu no Shinpo) 1966;10:744–50 [Japanese].
[29] Penfield W, Rasmussen T. Cerebral cortex of man. A clinical study of localization of function. New York: Hafner Publishing Company; 1968.
[30] Rustam R, Hamdi T. Methyl mercury poisoning in Iraq. A neurological study. Brain 1974;97:499–510.
[31] Semmes J, Weinstein S, Ghent L, Teuber HL. Somatosensory changes after penetrating brain wounds in man. Cambridge: Harvard University Press; 1960.
[32] Shiraki H, Takeuchi T. Minamata disease. In: Minckler J, editor. Pathology of the nervous system (II). New York: McGraw-Hill Inc; 1971. p. 1651–65.
[33] Study Group of Minamata Disease. Minamata disease. Kumamoto: Kumamoto University; 1968.
[34] Takeuchi T. Pathology of Minamata Disease. In: Study Group of Minamata Disease, editor. Minamata Disease. Kumamoto: Kumamoto University, 1968: 141–228.
[35] Takeuchi T, Eto K, Tokunaga H, Takizawa Y. Mercury levels of brain, liver and kidneys and pathological change grades of brains in all cases of Minamata disease autopsy from 1956 to 1989. Shokei Gakuen College Bulletin, vol. 23; 1991. p. 9–31.
[36] Tamashiro H, Arakai M, Akagi H, Futatsuka M, Roht LH. Mortality and survival for Minamata disease. Int J Epidemiol 1985;14:582–8.
[37] Tatetsu S. Psychiatric symptoms of Minamata disease. In: Study Group of Minamata Disease, editor. Minamata Disease, a Japanese-language edition. Kumamoto: Kumamoto University, 1968: 148–177 (Japanese).
[38] Tokuomi H. Clinical Investigation on Minamata Disease. A. Minamata Disease in Human Adult. In: Study Group of Minamata Disease, editor. Minamata Disease. Kumamoto: Kumamoto University, 1968: 37–72.
[39] Tokuomi H, Uchino M, Imamura S, Yamanaga H, Nakanishi R, Ideta T. Minamata disease (organic mercury poisoning): neuroradiologic and electrophysiologic studies. Neurology 1982;32:1369–75.
[40] Tomiyasu T, Nagano A, Yonehara N, Sakamoto H, Rifardi, Oki K, et al. Mercury contamination in the Yatsushiro Sea, south-western

Japan: spatial variations of mercury in sediment. Sci Total Environ 2000;257:121–32.
[41] Vahter M, Mottet NK, Friberg L, Lind B, Shen DD, Burbacher T. Speciation of mercury in the primate blood and brain following long-term exposure to methyl mercury. Toxicol Appl Pharmacol 1994;124:221–9.
[42] Victor M, Adams RD. Disorders of sensation. Sensory loss due to lesion in the parietal lobe. In: Wintrobe MM, Thorn GW, Adams RD, Braunwald E, Isselbacher KJ, Petersdorf RG, editors. Harrison's principles of internal medicine 7th edition. Tokyo: McGraw-Hill Kogakusha Ltd; 1974. p. 110–6.
[43] von Burg R, Rustam H. Electrophysiological investigations of methylmercury intoxication in humans evaluation of peripheral nerve by conduction velocity and electrography. Electroencephalogr Clin Neurophysiol 1974;37:381–92.
[44] von Economo C. The cytoarchitectonics of the human cerebral cortex. London: Humphrey Milford Oxford University Press; 1929.
[45] Weinstein S. Intensive and extensive aspects of tactile sensitivity as a function of body part, sex, and laterality. In: Kenshalo DR, editor. The skin senses. Springfield: Charles C ThomasIPublisher; 1968. p. 195–222.
[46] WHO. Environmental health criteria: 1. Mercury. Geneva: World Health Organization; 1976.
[47] WHO. Environmental health criteria 101: methylmercury. Geneva: World Health Organization; 1990.
[48] Windebank AJ. Peripheral neuropathy due to chemical and industrial exposure. In: Mattews WB, editor. Handbook of clinical neurology, vol. 7 (51), neuropathies. Amsterdam: Elsevier Science Publisher BV; 1987. p. 263–92.
[49] Windebank AJ, McCall JT, Dyck PJ. Metal neuropathy. In: Dick PJ, Thomas PK, Lambert EH, Bunge R, editors. Peripheral neuropathy. Philadelphia: W.B. Saunders Company; 1984. p. 2133–61.