The Severity of Minamata Disease Declined in 25 Years: Temporal Profile of the Neurological Findings Analyzed by Multiple Logistic Regression Model

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Minamata disease (MD), the first mass methylmercury poisoning in history, was caused by ingesting seafood from methylmercury-contaminated areas of Minamata Bay and the neighboring seas in Japan (Kutsuna 1968; Irukayama 1977). Fifty years have passed since the official discovery of MD in 1956. The core symptoms and signs of MD have been considered to be “glove-and-stocking type” sensory disturbances, ataxia, concentric constriction of visual fields, and hearing...
impairment (Tokuomi et al. 1961, 1968). One hundred and eleven patients in Minamata developed this disease between 1953 and 1962. Thereafter, 2,154 patients were confirmed between 1963 and 2003. Of the certified patients with MD, 2/3 of them are already dead. In the survivors, the majority of patients belong to chronic MD which showed an insidious onset after 1960 with mild or vague neurological manifestation (Takeuchi and Eto 1999; Uchino et al. 2001), and pathological findings have been modified by aging and various complications (Uchino et al. 1995). Concerning the temporal profile of neurological findings in MD, there have been neurosymptomatological studies on the prevalence rate of each symptom and sign (Okajima et al. 1976; Tokuomi et al. 1980; Tokuomi et al. 1982) but no detailed studies on the possible correlation among neurological findings or importance of each symptom and sign. To clarify differences in the severity of MD, a statistical method by calculating discriminants in patients certified as MD is needed to be developed.

In this study, we established such methods to clarify the possibility and the severity of MD. Using the established method, we also carried out a survey of neurological findings and complications in certified survivors to assess the present status. In addition, neurological findings and complications at the time of medical examination of these patients were investigated based on data of the Minamata Disease Victims Certification Council and compared with the data obtained in the present survey. The temporal profiles of clinical findings in certified patients with MD were evaluated.

**Subjects and Methods**

To develop a discriminant value which indicates the possibility and severity of MD, a multiple logistic regression model was established. The neurological signs and symptoms of 1,617 applicants (479 from Kumamoto, 168 from Kagoshima, and 970 from Niigata) for MD before 1972, including certified MD patients from Kumamoto (n = 412), Kagoshima (n = 103), and Niigata (n = 525), were evaluated. A total of 1,200 residents in Kasari district whose life style being similar with the Minamata and Izumi district but lives on seafood not exposed to methylmercury, was used as control. Neurological symptoms and signs were compared between the applicants of MD and control in terms of 39 items closely associated with the differentiation of methylmercury intoxication. Sensory disturbances were expressed using a 5-grade system (sensory disturbances distributed below wrist and ankle: 1, below elbow and knee: 2, below shoulder and thigh: 3, whole body: 4, absent: 0), and other symptoms were expressed using a 2-grade system (present: 1, absent: 0).

The diagnostic model for discrimination was calculated with neurological findings as independent variables, and applicants or residents in un-polluted area as dependent variable. The items used as independent variables in the first method were as follows: sensory disturbance around mouse, facial nerve palsy, dysarthria, limitation of neck movement, Spurling’s sign, involuntory movement of the upper extremities (U/E), muscle atrophy of U/E, weakness of U/E, muscular tonus abnormality of U/E, dysdiadochokinesis, impairment of finger-to-nose test, laterality of U/E, muscle atrophy of the lower extremities (L/E), muscular tonus abnormality of L/E, weakness of L/E, impairment of heel-knee test, laterality of L/E, glove-and-stocking type sensory disturbances, hemisensory disturbance, radicular distribution of sensory disturbance, hyperreflexia of biceps reflex, hyporeflexia of biceps reflex, hyperreflexia of triceps reflex, hyporeflexia of triceps reflex, hyperreflexia of radial reflex, hyporeflexia of radial reflex, hyperreflexia of knee jerk, hyporeflexia of knee jerk, hyperreflexia of ankle reflex, hyporeflexia of ankle reflex, Babinski’s sign, laterality in deep tendon reflex, Romberg’s sign, constriction of visual field, laterality of visual field, disturbance of extraocular movement, nystagmus, decrease of mean hearing ability, and laterality of hearing ability. Age and gender were used as covariates. The first method was developed for applicants from Kumamoto, Kagoshima, and Niigata, respectively. Each method was named as the first Kumamoto method, the first Kagoshima method, and the first Niigata method.

The second method of predictive index of MD was produced by laying stress on sensory disturbances, impairment of heel-knee test and finger-to-nose test, and constriction of visual field which are core symptoms and signs of MD. The second method was also developed for applicants from Kumamoto, Kagoshima, and Niigata.

The third method of predictive index of MD was also made using only “glove-and-stocking type” sensory
disturbances as an independent variable. This method was also developed for the applicants from the 3 prefectures.

Using discriminants by multiple logistic analysis that were obtained in certified patients in Kumamoto, Kagoshima, and Niigata, the temporal profile in the severity of MD from the time of certification to the survey in 2003 and the influences of complications were evaluated.

Then, a follow-up survey was conducted to evaluate the present neurological symptoms and signs, the status of complications, and ADL in patients in the Minamata and Izumi district who were being treated on an outpatient basis in the Minamata City General Hospital and Medical Center. The subjects were consisted of 3 typical MD patients with the core MD symptoms who survived the period of acute methylmercury intoxication before 1960, 21 chronic MD patients who showed an insidious onset after 1960 with mild and vague neurological symptoms, and 1 fetal MD patient. As the 2/3 of the certified MD patients with the most severe symptoms died before this survey, this study was essentially based on the survivors. In addition, data obtained in this survey were compared with neurological findings obtained from examination records/data in the Minamata Disease Victims Certification Council at the time of recognition about 20 years earlier, and the temporal profile was evaluated.

**ETHICAL CONSIDERATION**

We informed the subjects that this study deals with the clinical symptoms and signs of individual certified patients, but that obtained results represent the characteristics of neurological symptoms of the group as a whole and cause no disadvantages in individual patients, and asked them for their cooperation in examinations after obtaining their adequate understanding of the purpose of this study. Before producing a database, data in the Minamata Disease Victims Certification Council such as names and birth dates that allow the identification of patients were completely eliminated and made anonymous to protect the privacy of individual subjects.

**RESULTS**

**Establishment of predictive index**

The first method of predictive index of MD in Kumamoto is as follows:

Male: \[ \text{logit} (Y) = 15.043 - 0.279 a + 2.301 b + 3.278 c + 2.790 d + 2.605 e + 3.261 f - 2.093 g + 1.135 h + 2.137 i + 3.025 j - 2.580 k + 4.11 L \]

Female: \[ \text{logit} (Y) = 14.415 - 0.269 a - 0.554 b + 1.965 c + 1.170 e + 0.365 f + 1.018 g + 1.182 h + 1.921 i + 3.274 j - 2.049 k + 4.733 L \]

\( a: \) age at examination, \( b: \) dysarthria, \( c: \) muscle atrophy of U/E, \( d: \) impairment of heel-knee test, \( e: \) laterality of incoordination in U/E, \( f: \) muscle atrophy of L/E, \( g: \) hyperreflexia of radial reflex, \( h: \) hyporeflexia of knee jerk, \( i: \) constriction of visual field, \( j: \) decrease of mean hearing ability, \( k: \) laterality of hearing ability, \( L: \) glove-and-stocking type sensory disturbances

Likewise, the first Kagoshima method is as follows:

Male: \[ \text{logit} (Y) = 11.965 - 0.285 a + 1.192 b + 1.225 c + 0.824 d - 0.654 e - 0.094 f + 1.228 g + 4.021 h + 3.447 i + 4.065 j \]

Female: \[ \text{logit} (Y) = 11.484 - 0.287 a + 2.057 b + 2.001 c + 1.697 d + 1.610 e + 2.829 f + 1.426 g + 3.738 h + 3.699 i + 2.969 j \]

\( a: \) age at examination, \( b: \) dysarthria, \( c: \) limitation of neck movement, \( d: \) disturbed heel-knee test, \( e: \) laterality of U/E, \( f: \) muscle atrophy of the L/E, \( g: \) weakness of L/E, \( h: \) glove-and-stocking type sensory disturbances, \( i: \) constriction of visual field, \( j: \) decrease of mean hearing ability.

The first Niigata method is as follows:

Male: \[ \text{logit} (Y) = 12.839 - 0.245 a + 3.268 b + 2.886 c + 4.600 d + 2.798 e - 2.033 f + 1.999 g + 1.585 h - 2.300 i \]

Female: \[ \text{logit} (Y) = 13.722 - 0.256 a + 1.862 b + 1.923 c + 5.317 d + 3.605 e - 0.871 f + 1.887 g - 1.409 h - 2.362 i \]

\( a: \) age at examination, \( b: \) impairment of heel-knee test, \( c: \) laterality of U/E, \( d: \) glove-and-stocking type sensory disturbance, \( e: \) decrease of mean hearing ability, \( f: \) Spurling’s sign, \( g: \) radicular distribution of sensory disturbance, \( h: \) hyporeflexia of radial reflex, \( i: \) laterality of hearing ability.

The second Kumamoto method is as follows:

Male: \[ \text{logit} (Y) = 1.465 - 0.127 a + 4.804 b + 3.056 c + 2.304 d + 3.485 e + 2.394 f \]
+ 4.229 g – 3.216 h + 3.118 i
Female: logit (Y) = 6.746 – 0.187 a
+ 2.387 b + 1.877 c + 1.524 d + 2.757 e
+ 2.924 f + 3.088 g – 1.387 h + 0.667 i

a: age at examination, b: sensory disturbance around mouth, c: limitation of neck movement, d: tremor, e: dysdiadochokinesis, f: disturbance of ocular movement, g: decrease of mean hearing ability, h: laterality of hearing ability, i: hyporeflexia of biceps reflex

The second Kagoshima method is as follows:
Male: logit (Y) = 0.672 – 0.201 a + 3.397 b
+ 3.238 c + 4.284 d + 8.770 e + 1.808 f
+ 2.304 g
Female: logit (Y) = 2.978 – 0.132 a
+ 3.247 b + 1.674 c + 3.082 d + 3.004 e
− 0.298 f − 0.317 g


The second Niigata method is as follows:
Male: logit (Y) = −0.658 – 0.092 a + 3.217 b
+ 2.275 c + 1.781 d + 4.600 e + 1.994 f
− 3.129 g + 2.948 h + 3.289 i − 1.108 j
Female: logit (Y) = −0.627 – 0.073 a
+ 3.771 b + 2.590 c + 0.053 d + 4.089 e
+ 0.251 f − 2.415 g + 1.561 h + 2.663 i
+ 0.912 j


The third Kumamoto method is as follows:
Male: logit (Y) = 6.001 – 0.146 a + 7.173 b
Female: logit (Y) = 7.816 – 0.167 a
+ 6.797 b

The third Kagoshima method is as follows:
Male: logit (Y) = 6.989 – 0.161 a + 5.621 b
Female: logit (Y) = 7.660 – 0.164 a + 5.128 b

The third Niigata method is as follows:
Male: logit (Y) = 13.601 – 0.237 a + 6.001 b
Female: logit (Y) = 11.585 – 0.202 a + 5.440 b

a: age at examination, b: glove-and-stocking type sensory disturbances.

Complications of MD
In the 32 outpatients (age, 71.0 ± 13.0 years: 25 certified patients in Kumamoto Prefecture and 7 in Kagoshima Prefecture) of the Minamata City General Hospital & Medical Center, cerebral infarction was the most frequent complication (Table 1), being observed in 13 patients (age, 78.8 ± 9.4 years). The clinical type of cerebral infarction could be determined in 8 patients, being lacunar infarction in 6 patients (age, 76.2 ± 9.8 years), atherothrombotic brain infarction in 1 (76 years), and cardiogenic brain embolism in 1 (96 years). As other frequent complications, tension type headache was observed in 9 patients (age, 71.7 ± 12.6 years), cervico-omo-brachial syndrome in 7 (72.1 ± 11.2 years), and spondylitis deformans in 6 (76.0 ± 8.9 years); many patients had problems in skeletal organs. As medical complications, hypertension was observed in 7 patients (age, 76.5 ± 12.4 years), and gastrointestinal complications such as atrophic gastritis and duodenal ulcer in 6 (69.7 ± 11.8 years).

As other complications, cerebellar degeneration (late cerebellar cortical atrophy: LCCA) was present in 1 patient (age, 76 years; 62 years at the onset after recognition), and HTLV-I (human T-cell leukemia virus type I)-associated myelopathy (HAM) in 2 (ages, 67 and 75 years).

Changes in discriminant scores
In the 25 patients (age, 71.3 ± 13.1 years) for whom neurological symptoms and signs at the time of certification could be clarified based on data in the Minamata Disease Victims Certification Council or examination records, changes in the discriminant score were evaluated. The mean duration between the time of certification and this survey in 2003 was 25.5 ± 6.6 years. First, changes in the discriminant score obtained by the first method were evaluated (Fig. 1). The first Kumamoto method showed a discriminant score of ≥ 80 at the time of certification in 24 patients, after excluding 1 certified in Kagoshima Prefecture, but its decrease in most
patients at the time of the survey in 2003 (median value: 99.998 → 35.427). The first Kagoshima method showed a discriminant score of ≥ 90 in 22 patients, while the first Niigata method showed a discriminant score of ≥ 80 in 23 patients at the time of certification. Both the Kagoshima and Niigata methods revealed a decrease in the discriminant score at the time of the survey in 2003 (median value: Kagoshima method; 99.972 → 2.935; Niigata method, 99.969 → 59.282). When

<table>
<thead>
<tr>
<th>Table 1. Concomitant diseases observed in patients with minamata disease</th>
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<tr>
<td><strong>Number of Patients</strong></td>
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<tr>
<td>Brain Infarction</td>
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<td>Atherothrombotic</td>
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<td>Cardioembolic</td>
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<td>Brain Hemorrhage</td>
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<td>Orthopaedic Diseases</td>
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<td>Cervico-omobrachial syndrome</td>
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<td>Cervical spondylosis</td>
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<td>Spondylosis deformans</td>
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<td>Periarthritis scapulohumeralis</td>
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<td>Osteoarthritis</td>
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<td>Bone fracture (L/E)</td>
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<td>Osteoporosis</td>
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<td>Rheumatic disease</td>
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<td>Functional Disorder</td>
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<td>Tension type headache</td>
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<td>Vertigo</td>
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<td>Others</td>
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<td>HTLV-I related myelopathy</td>
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<td>Late Cortical Cerebellar atrophy</td>
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<td>Parkinsonism</td>
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<td>Involuntary movement</td>
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<td>Dementia</td>
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<td>Depression</td>
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<td>Sleeplessness</td>
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<td>Cancer</td>
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<td>Benign Prostate Hyperplasia</td>
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changes in the discriminant score in each patient were evaluated, only 1 patient (Patient A) showed increases in the discriminant score by all of the first Kumamoto method, Kagoshima method, and Niigata method (Fig. 1). Patient A had LCCA as a complication.

Next, changes in the discriminant score were evaluated by the second method obtained from the core symptoms and signs of MD (Fig. 2). At the time of recognition, the mean discriminant score was 70.483 ± 38.082 by the Kumamoto method, 57.832 ± 43.456 by the Kagoshima method.

![Fig. 1. Temporal profile of the predictive index score of Minamata Disease (the 1st method).](image1)

Closed circles represent the only patient (patient A) whose discriminant score increased in 14 years.

![Fig. 2. Temporal profile of the predictive index score of Minamata Disease (the 2nd method).](image2)
method, and $55.460 \pm 34.351$ by the Niigata method, showing marked dispersion (standard deviation, 34-43) by each method. The discriminant score had decreased at the time of the survey in 2003 in most patients, which was similar to the results of the first method (median value: Kumamoto method, 94.770 → 5.364; Kagoshima method, 82.724 → 1.250; and Niigata method, 61.098 → 10.372). Evaluation of changes in each patient by the second Kumamoto method showed no change or a decrease in 21 patients, a discriminant score of $\geq 90$ at the time of certification and a further increase in 2003 in 2, a discriminant score of $\leq 20$ at the time of certification and an increase to $\leq 20$ in 2003 in 1, and a discriminant score of $\leq 20$ and an increase to 62.966 in 2003 in 1 (Patient B). By the second Kagoshima method, the discriminant score decreased in 22 patients. The discriminant score by this method increased in 3 patients, but the change was slight; being $\geq 99$ in 1 patient and $\leq 5$ in the other 2 at the time of both recognition and survey in 2003.

The third method is based on only ‘glove-and-stocking type’ sensory disturbances (Fig. 3). The discriminant score at the time of certification by the third Kumamoto method was $\leq 10$ in 2 patients certified in Kagoshima. At the time of the survey in 2003, the discriminant score had decreased in all patients, being $< 20$ (median value: 99.637 → 0.254). The third Kagoshima method and the third Niigata method showed a general tendency to decrease (median value: Kagoshima method, 98.675 → 10.852; Niigata method, 99.933 → 52.891), but changes in each patient varied, showing a decrease, no change, or an increase.

In a representative patient (aged 14 years at the time of certification in Kumamoto Prefecture and 47 years at the survey in 2003), changes in the discriminant scores obtained by the first-third methods are shown in Fig. 4. The discriminant score decreased by some methods but was unchanged by others, which reflects differences due to importance of neurological symptoms and signs. Patient A (aged 63 years at the certification in Kagoshima Prefecture and 77 years at the survey in 2003), in whom the discriminant score increased by all the first Kumamoto, Kagoshima, and Niigata methods, developed LCCA at the age of 62 years. In this patient, the discriminant score was low at the time of certification but increased with aggravation of cerebellar ataxia (Fig. 5).

Fig. 3. Temporal profile of the predictive index score of Minamata Disease (the 3rd method).
Association between the patient’s age and discriminant score

As the predictive index scores of MD generally declined in about 25.5 years’ time, there might be a turning point of age starting deterioration in severity of MD. Moreover, the age related concomitant disorders increase with time. Therefore, the possible association between their chronological age at the time of examination and the discriminant score was compared in the same 25 patients. The distribution of discriminant scores by the first Kumamoto method (Fig. 6) and the first Kagoshima method revealed values near 100 in all patients aged ≤ 45 years and values ≤ 20 in patients aged > 45 years. The same tendency was observed by the second Kumamoto method, second Kagoshima method, third Kumamoto method, and the third Kagoshima
In Patient B, diagnosed as having typical MD (aged 47 years at the time of certification in Kumamoto Prefecture and 72 years at the survey in 2003), the discriminant score increased by the second Kumamoto method but was unchanged or decreased by the other methods. In a patient with fetal MD (aged 25 years at certification in Kagoshima Prefecture and 44 years at the survey in 2003), the discriminant scores obtained by the first and second methods were near 100 at the time of both certification and survey in 2003.

**DISCUSSION**

In this study, we evaluated the present neurological findings and the temporal profile of the severity of MD in certified patients with MD using discriminants by multiple logistic analysis. Similar discriminant was produced by Igata in the certified patients of Kagoshima (Igata 1986), but non-certified ones in the same polluted area were used as controls. Our discriminants were obtained in certified patients in Kumamoto, Kagoshima, and Niigata using inhabitants in seaside area similar to Minamata district but not polluted by methylmercury as controls. The temporal profile in the severity of MD from the time of certification to the survey in 2003 and the influences of complications were evaluated. In addition, the status of complications was investigated, and the present status of patients with chronic MD 50 years after discovery was clarified. The mean age of the certified patients with MD in Minamata and Izumi district as the subjects was 70 years, showing the aging of patients with MD. Frequent disorders among the aged such as cerebral infarction, cervical spondylosis, cervico-omo-brachial syndrome, and spondylosis deformans were often observed, and the pathological findings of MD had been complicatedly modified by complications.

The probability of MD was evaluated using the discriminants established in this study. Because many patients with the most severe symptoms and signs with acute methylmercury intoxication died before our survey, only patients of lower severity might be included in this survey. In spite of such inevitable selection bias in our study design, the discriminant score was generally high by each method at the time of certification but had decreased in most patients at the time of the survey in 2003. This suggested alleviation of the symptoms and signs of MD after a course of about 25 years. The discriminant score and its temporal changes markedly differed among the discriminants used and were associated with weighted symptoms and signs. In other words, some symptoms and signs of MD such as sensory

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**Fig. 6.** Relationship between age and the predictive index score of Minamata disease (the 1st Kumamoto method).
- ○, Timing of Certification; ●, Follow up (2003).
disturbances were alleviated while others such as concentric contraction of visual fields and hearing impairment were not changed during the 25-year course.

Of the certified patients, only 1 patient showed definite aggravation of the discriminant score. This patient had developed LCCA in the previous year of certification, and the increase in the discrimination value may have been due to the progression of cerebellar ataxia associated with LCCA. It should be discussed whether this patient had MD complicated by LCCA or fulfilled the certification criteria (Director General of Environmental Health Department 1986) because sensory disturbances due to spondylosis deformans added to the cerebellar symptoms of LCCA. At least, the probability of MD is poor based only on the discriminant score at the time of certification.

These results suggest that MD is severest during the methylmercury exposure period and is alleviated with time after discontinuation of the exposure. When aggravation of neurological symptoms is observed, the influences of complications may be marked.

Evaluation of the age at the time of examination and the distribution of discriminant scores suggested changes in the pathological condition of MD at the age of 45 years. At the age of ≤ 45 years, the discriminant score was close to 100. At the age of > 45 years, the discriminant score indicates that the probability of MD is poor. One factor may be the modification of the pathological condition due to an age-associated increase in the incidence of complications.

Among the subjects in this study, a patient with classic MD was compared with a patient with fetal MD. The discriminant score in the patient with fetal MD did not change from the time of certification to the survey in 2003. In contrast, the patient with classic MD (certified at the age of 47 years) showed alleviation of symptoms and signs. It is unclear whether these findings reflect the development of irreversible neuronal damage induced by methylmercury exposure during the fetal period, or whether symptoms decrease after the age of 45 years even in the presence of fetal MD. Consideration should also be given to the time of methylmercury exposure (fetal period or after birth, childhood or adulthood), and the duration and amount of exposure. In patients with fetal MD, further continuous evaluation of neurological findings is necessary.

When the third Kumamoto method based only on ‘glove-and-stocking type’ sensory disturbances was used to evaluate the probability and severity of MD, all patients showed a very low discriminant score (< 20) at the time of survey in 2003. This suggests that the differentiation of chronic Minamata disease due to methylmercury based only on sensory disturbances is difficult. We believe that the precise diagnosis of MD based on the distribution of sensory disturbances is essentially unachievable, especially in the aged patients.

In conclusion, the established predictive index score of MD, which indicates the probability and the severity of MD, usually declined in 25 years. It was the age-related concomitant disorders that caused the deterioration of neurological findings in patients aged over 45 year.

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References