Neurologic Features of Chronic Minamata Disease (Organic Mercury Poisoning) Certified at Autopsy

Makoto Uchino, Toru Okajima*, Komyo Eto**, Toshihide Kumamoto***, Isao Mishima* and Masayuki Ando

To better understand the neurologic events related to chronic Minamata disease (organic mercury poisoning), we studied data from 77 patients with Minamata disease as certified at autopsies performed from 1976 to 1994 (mean age: 72.3 years). Major neurologic findings included: sensory impairment in 80.5% of the patients which was limited to the extremities in 42.9%. Impairment of lower extremity coordination was present in 35.8% of the patients, constriction of the visual fields in 28.8%, and retrocochlear hearing loss in 15.3%. There was no correlation between the degree of cerebellar incoordination and the methylmercury concentration in the cerebellum. Compared with the classic type of Minamata disease, the incidence of major neurologic findings was markedly decreased. In light of these findings, supplemental examinations including brain computed tomography (CT), magnetic resonance imaging (MRI), short latency somatosensory evoked potential (SSEP), or tremogram may be necessary to clinically diagnose Minamata disease, especially in atypical or mild cases.

(Key words: Minamata disease, autopsy, visual constriction, cerebellar incoordination, methylmercury concentration)

Introduction

Minamata disease, the first mass methylmercury poisoning in history, was caused by the ingestion of seafood from methylmercury-contaminated areas of Minamata Bay and the neighboring seas in Japan (1, 2). Residents of that area first showed evidence of the disease in 1953 (3, 4). They experienced concentric construction of their visual fields, hearing loss, tremors, cerebellar incoordination, and sensory impairment of their tongue and lips or extremities. These findings are consistent with the features of organic mercury poisoning first described by Hunter et al in 1940 (5) and Hunter and Russell in 1954 (6). One hundred and seventy-eight patients in Minamata fell victim to this disease from 1953 to 1962, 144 from 1963 to 1972 and 1,935 between 1973 and 1994. For over 40 years, our colleagues have performed studies on Minamata disease patients, with special attention directed towards new or shifting symptoms (7–9). To better comprehend the characteristic neurologic features of chronic Minamata disease of late-onset, we investigated the neurologic findings in patients who were examined by neurologic prior to death and at autopsy.

Subjects and Methods

Based on data obtained from the Kumamoto Certification Council for pollution-related injuries in patients, neurologic status was determined using data from 77 Japanese patients with Minamata disease, as certified by autopsies performed from 1976 to 1994. This cohort consisted of 55 men and 22 women aged 36 to 96 years (mean: 72.3 years). The cerebral pathology in these patients was assigned to one of six grades classified by Takeuchi and Eto et al (10–14). All of the cases were classified as Grade I except for 4 cases of Grade II. The decrease in the number of neurons (“thinning-out”) in the cortex was <30% in Grade I. In the 4 cases of Grade II, a 30 to 50% decrease in the number of neurons was evident in the vulnerable areas of the cerebral cortices. Glial cells, particularly astrocytes and macrophages, were increased in “thinning-out” areas of neurons. Changes in the cerebellum were consistent with Grade I in the classification system of Takeuchi and Eto (13, 14), except for one patient in whom the loss of granule cells was relatively well-recognized and apical scar formation also apparent. Irregularity of the Purkinje cell layer also was clearly recognized and there was a slight gliosis with Holzer staining in

From the First Department of Internal Medicine, Kumamoto University School of Medicine, Kumamoto, *Jonan Hospital, Kumamoto, **National Institute for Minamata Disease, Minamata and ***the Third Department of Internal Medicine, Oita Medical University, Oita
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Reprint requests should be addressed to Dr. Makoto Uchino, the First Department of Internal Medicine, Kumamoto University School of Medicine, 1-1-1 Honjo, Kumamoto 860

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this irregular area. Histochemically, mercury was identified in nerve cells and macrophages in the brain (15). In peripheral nerves, the posterior roots, particularly in the lumbar area, demonstrated some degree of abnormality in all patients. Changes in the anterior roots were less than those in the posterior roots. Methylmercury concentrations in the cerebellum (vermis) were measured by gas chromatography in 45 patients, and the correlation between the cerebellar methylmercury concentration and the degree of cerebellar incoordination was evaluated by determining the absence (=0), suspicion (=0.5), or presence (=1.0) of ten cerebella signs including: dysarthria, dysdiadochokinesis, impairment in finger-to-nose test, heel-to-knee test, and shin tap test, standing disturbance, dysstasia affecting one leg, impairment in simple gait and tandem gait, and intention tremor. The incidences of major neurologic features between classic Minamata disease patients reported by Tokuomi et al (7–9) were compared with diseases certified by autopsy.

Results

Table 1 summarizes the incidence of major neurologic features in these 77 patients. The cardinal symptoms of construction and depression of the visual fields were present in 28.8% and 50.0% of the patients, respectively. Hearing disorders included definite or possible retrocochlear deafness with deterioration in speech-hearing and auditory fatigue in 9/59 patients (15.3%); probable labyrinthine deafness with recruitment was noted in 22/59 patients (37.3%). Impaired cerebellar coordination was infrequent, including adiadochokinesis and impairment on the finger-to-nose, heel-to-knee, shin tap tests observed in 17.6%, 29.0%, and 35.8% of the patients, respectively. Findings suggestive of a sensory disorder were found in 62/77 patients (80.5%). These sensory disorders included: a "glove and stocking" type of hypesthesia (extremities type) in 33 patients (42.9%), systemic tactile and pain hypesthesia or anesthesia (systemic sensory disorder type) in 7, a hemisensory disorder in 9, an alternative sensory disorder (segmental sensory disorder or irregular type) in 10 and no impairment of superficial sensation in 15 patients. Figure 1 illustrates the

![Figure 1. Relationship between the methylmercury concentration in the cerebellum (ppm) and the grade of cerebellar incoordination. *Each grade was determined as the total score (absence (=0), suspicion (=0.5), and presence (=1.0)) of ten cerebellar signs: dysarthria, dysdiadochokinesis, impairment in finger-to-nose test, heel-to-knee test, and shin tap test, standing disturbance, dysstasia affecting one leg, impairment in the simple and tandem gait, and intention tremor.](image-url)
The classic type of Minamata disease includes those with a relatively acute or subacute onset from 1957–1960, corresponding to the period when seafood in Minamata Bay was heavily contaminated with methylmercury. Most patients suffered from concentric constriction of their visual fields, hearing loss, cerebellar ataxia, and a “glove and stocking” type of sensory disturbance, and hence were clinically diagnosed with methylmercury poisoning (Minamata disease). Follow-up studies were performed by Tokuomi et al from 1957 to 1960 (34 cases, mean age: 40.7 years), in 1969 (22 cases), and in 1978 (13 cases, mean age: 48.4 years) (7–9). Classic patients demonstrated concentric constriction of their visual fields (82%), hearing loss (80%), cerebellar incoordination (70%), and “glove and stocking” types of sensory disturbance (100%) even 20 years after disease onset (9). On the other hand, the subjects who were later diagnosed by autopsy had only complained of symptoms including: the gradual development of a sensory disturbance, leg weakness, headache, dizziness, a decrease in visual acuity, and hearing loss from 1957–1975; only rarely were these findings considered to be evidence of Hunter-Russell syndrome.

Discussion

The classic type of Minamata disease patients and those with disease certified by autopsy.

Table: Comparison of incidences of major neurologic features between classic Minamata disease patients and those with disease certified by autopsy.

- Visual field constriction
- Hearing disorders
- Dysarthria
- Incoordination
- Dysdiadochokinesis
- Impairment in finger-to-nose test
- Impairment in heel-to-knee test
- Impairment in shin tap test
- Postural & gait disturbance
- Standing disturbance
- Dysstasia affecting one leg
- Positive Romberg test
- Simple gait disturbance
- Tandem gait disturbance
- Intention tremor
- Deep tendon reflexes
- Increased
- Decreased/absent
- Sensory disorder
- Superficial sensation (glove & stocking)
- Deep sensation

Figure 2. Comparison of incidences of major neurologic features between classic Minamata disease patients and those with disease certified by autopsy.

correlation between the methylmercury concentration in the cerebellum (ppm) and the degree of cerebellar incoordination in 45 patients. The coefficient of correlation (r) was 0.106 (not significant).
From 1981–1985, we analyzed neurologic features and complications in 171 patients with clinically documented Minamata disease who resided in Kumamoto Prefecture (16, 17). We found an increased incidence of Minamata disease patients presenting with mild and infrequent cardinal neurologic findings, such as constriction of the visual fields, hearing loss, and cerebellar ataxia; an increased incidence of age-related complications was also noted. However, we have reported that the incidences of these complications (except for retinitis pigmentosa) differ little from the corresponding prevalences of these symptoms in the general population (17).

In the present study, we investigated the neurologic findings in 77 Minamata disease patients, as certified by autopsies performed between 1976–1994 and compared these findings with those of classic Minamata disease patients reported by Tokuomi et al from 1957–1960 (1, 2, 7). Classic patients previously have demonstrated concentric constriction of visual fields in 82%, hearing loss (80%), cerebellar incoordination (70%), and sensory disturbance (100%) even 20 years following disease onset. However, in the present study, cardinal neurologic features such as concentric constriction of the visual fields and cerebellar ataxia accounted for less than 50% of findings, except for dysstasia affecting one leg and a tandem gait disturbance. Most symptoms were mild except for sensory impairment. Although the incidence of abnormal deep tendon reflexes was increased in autopsy cases, it may be due to the increased incidence of age-related complications such as cerebrovascular disease and cervical spondylosis, or diabetes (18). Compared with the data reported in the 1981–1985 survey, the incidence of main neurologic features in patients with this disease has decreased. In cases of acute intoxication with organic mercury, there is a correlation between the volume of ingested contaminated food and the severity of the clinical symptoms and signs (19). However, we found no correlation between the methylmercury concentration in tissues and the degree of clinical symptoms and signs in chronic Minamata disease patients. The biological half-life period of methylmercury is about 70 days and it is known that the methylmercury contents decrease and reveal nearly normal levels in the brain of mild prolonged cases with Minamata disease (13). We also found that these 77 patients with Minamata disease showed no significant difference in the frequency of main neurologic features except for visual constriction and sensory disorder from 78 non-Minamata disease cases who resided in Minamata district but had no characteristic pathology of Minamata disease (unpublished data). The presence of Grade I pathologic lesions (30% of “thinning-out” of neurons) may not be related to the typical neurologic findings of organic mercury poisoning. Thus, it is difficult to make a precise clinical diagnosis of Minamata disease, in atypical or mild cases and supplemental examinations including: brain CT, MRI, somatosensory evoked potential (SEP), or tremogram are necessary to confirm the clinical diagnosis in such cases (20).

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References