

## Congenital Minamata disease: a description of two cases in Niigata

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### Abstract

*Minamata disease or methyl mercury poisoning from industrial pollution was first described from Minamata, Japan in the 1950s. Subsequently, a similar poisoning episode occurred at Niigata, Japan in the 1960s. This paper describes the Minamata event and then presents two case reports believed to be prenatal poisoning from consumption of contaminated fish at Niigata. Case number one is of special interest because it is the only subject with congenital Minamata disease for whom exposure was actually measured near the time of birth.*

**Key words** mercury, methyl mercury, Minamata disease, fish consumption, prenatal poisoning

### The background

#### Recognition of Minamata disease

In 1956, several patients with an unusual illness were admitted to the hospital affiliated with the Minamata factory of Shin Nihon Chisso Corporation. Their symptoms and signs indicated a disorder in the central nervous system, but the cause was unknown. Evaluations failed to provide an answer and so an ad hoc committee was formed to determine the cause and recommend the most effective treatment. The committee included representatives of the following five groups: 1) the Minamata Health Centre; 2) the hospital attached to the Chisso Corporation; 3) the Minamata Medical Association; 4) the Minamata City Hospital; and 5) the Minamata City Public Health Office. The committee was organized under the joint auspices of the Sanitary Division of the Kumamoto Prefectural Government to whom the outbreak was reported and the Division for Prevention of Epidemics within the Ministry of Welfare. The Medical Department of Kumamoto University was asked to study the disease. The university organized a research group under the leadership of Dr. M. Ozaki who was the dean of the Medical Department. The committee's research established beyond any doubt that the cause of the disorder inflicting such serious damage on the central nervous system was organic mercury.

#### Recognition of congenital or prenatal Minamata disease

In 1958, Dr. Kitamura from the Public Health Department at Kumamoto University noted that there were many children in and around Minamata who appeared to have cerebral palsy (1). Most of these children were born after 1955, but even among those born prior to that year the incidence was considered high. Some reports estimated the incidence of cerebral palsy in the Minamata area to be as high as 20-58 per 1000 children (2). In contrast, the incidence of cerebral palsy in Japan as a whole at that time was generally believed to be about 1-2 per 1000 children. In addition, studies of primary school children indicated a high incidence of motor disabilities (3). Among the families Dr. Kitamura examined,

some mothers seemed healthy while others had signs or symptoms of Minamata disease.

### Clinical studies

In the early 1960s, Nagano and colleagues (4) and Harada (5) from the Departments of Paediatrics and Neuropsychiatry at Kumamoto University Medical School carried out clinical studies of children. Two reports described the characteristic symptoms common to all the affected cases (5-6). These included intellectual impairment, persistence of primitive reflexes (sucking, rooting, grasping and crossed extension), cerebellar signs, and delayed physical development. In addition, many of the children had hypo- or hyperkinesias, drooling, strabismus, pyramidal signs, and personality disorders. According to Takeuchi, (7) growth failure was striking. One of the two children he studied at autopsy (see below) had a height and weight only half that of the controls while the other weighed only one third as much. In contrast, weight loss was not observed in adults with Minamata disease. The children's growth limitations were attributed to the prenatal mercury intoxication. Among Harada's subjects a similar observation was made, but in a few cases growth appeared normal at later ages. One of Harada's patients weighed only 18 kg at the age of 18 years (5). Harada postulated that difficulty with chewing and swallowing as well as lesions in the central nervous system involving areas responsible for endocrine functions might contribute to the growth failure.

### Pathological studies

In 1961, Morikawa in the Department of Pathology at Kumamoto University published an animal experiment (8). He gave MeHg to a cat during gestation. The cat subsequently delivered three kittens. One kitten exhibited a remarkable ataxia and at autopsy showed distinct histological lesions in the cerebrum and cerebellum.

In 1963, autopsies were performed on two children who had had cerebral and cerebellar symptoms (7). These studies led Takeuchi, also from the Pathology Department at Kumamoto University, to conclude that they suffered from prenatal poisoning with MeHg or congenital Minamata disease. He based his conclusion on the following findings.

1) The quantity of mercury in the mother's hair was 20 to 40 times higher than that of controls. 2) The pathological changes observed in the brain were primarily in the cerebral cortices and the granular layer of the cerebellum. The primary change in the cerebral cortex was loss of neurons and damage to the precentral and postcentral gyri (motor and sensory cortex respectively), the calcarine or visual cortex, and the auditory cortex. Changes in the cerebellum consisted mainly of a reduced number of granule cells. Only minimal pathological changes were seen in the brainstem, spinal cord and peripheral nerves. Both hypoplasia and dysplasia of the cerebral cortex were also observed. These changes were characteristic of those seen following MeHg poisoning. 3) There was also substantial brain atrophy. One brain was two-

thirds of the normal weight while the other was only half the normal.

Matsumoto reported these results to the General Assembly of the Kumamoto Medical Association (9). In 1963, based on the above results, he concluded that the two children had been poisoned with MeHg transferred across the placenta and thus the disease should be referred to as congenital Minamata disease.

### Criteria for the clinical diagnosis

According to Harada who first reported congenital Minamata disease in the English scientific literature, the disorder was characterized by intellectual impairment and motor dysfunction, especially cerebellar symptoms (10). Severe cognitive impairment was found in all subjects. In some subjects there were also persistent primitive reflexes, cerebellar ataxia, disturbances in physical development, dysarthria, and limb deformities. Most of the affected children also exhibited hyperkinesia (95%), hypersalivation (95%), seizures (82%), strabismus (77%), and pyramidal signs (75%).

### Broad recognition of the danger from pollution

In the early 1970s the photojournalist Eugene Smith introduced congenital Minamata disease to the world (11). He published pictures of the victims in the magazines *Life* and *Asahi Camera*. One photo in particular, that of a mother holding her 16-year-old girl in her arms while giving her a bath, was especially striking. The mother had eaten fish polluted with mercury before, during, and after the pregnancy, but the girl had never consumed fish. The girl had a rigid body with bent arms and crossed legs from her spastic muscles. She was confined to bed and had difficulty chewing and swallowing. She could neither move nor talk. She was diagnosed as having congenital Minamata disease because of a slight visual field constriction, paucity of movements and a left hemiparesis. She was the eldest daughter and her six siblings all appeared normal.

Her mother appeared healthy, but on medical examination she was found to have Minamata disease. She had paraesthesias of her hands and feet, headache, tremors, hearing loss and tired easily. She also had a slight visual field constriction, mild left hemiparesis and slowness to her movements. She had been treated for the arm and leg pains for nearly 10 years, but had not been diagnosed with Minamata disease. Her husband had some speech disturbance, but was not diagnosed with Minamata disease. The contrast between this mother and her child was striking and showed graphically the danger of environmental pollution with MeHg.

### Two manifestations of congenital Minamata disease in Niigata

Saito et al describe the circumstances that led to methyl mercury poisoning in Niigata, Japan, elsewhere in this issue (12). Two children suspected of having congenital Minamata disease were identified at Niigata. The courts officially acknowledged only one. The clinical histories of both subjects are presented here.

#### Case 1

CF was born on 27 March 1965 [Case 1 in group A in the paper by Saito et al this issue (12)]. The pregnancy and

delivery were normal and the mother denied taking any medication. At birth, CF weighed 3000 grams and appeared normal apart from slight jaundice. During infancy she had no significant illnesses. She was exclusively breast fed for the first two months, given mixed feeding with cow's milk / formula for the next six months, and then weaned to cow's milk. The family lived in Niizaki near the river and her father fished on the Agano River from October 1964 until March 1965. During the pregnancy with CF, her mother ate fish almost every day. The primary species consumed were Hemibarbus, Tribolodon, Zacco, and Carassiuses. She prepared the fish by boiling or roasting and sometimes would eat three or four carp of 30 to 40 cm in length in a day. Her father and an uncle who lived with the family were known to have Minamata disease.

CF and her mother (MF) had their hair mercury measured on multiple occasions using different methods. In June 1965, when CF was 1 month old, her hair mercury was 77 ppm by the dithizone method. At that time her mother's hair mercury level was 293ppm using a radioactive assay. CF had a subsequent hair analysis in October 1965 using an atomic absorption method that gave a result of 173 ppm and another in March 1967 using a radioactive assay indicating a level of 6.9 ppm. In November 1965 MF had her hair analysed again using dithizone, radioactive and atomic absorption assays. The findings were 80 ppm, 128 ppm and 177 ppm respectively. In March 1966 MF had a radioactive analysis of her hair that showed 28 ppm.

In September 1965 at about 4 months of age CF's parents noted that she did not attempt to take things with her hands. At the same time, her mother noted difficulty moving her own legs, numbness in the buttocks and distally in the extremities, and pains in her joints. The Neurological Department of Niigata University evaluated MF in October 1965. She was not diagnosed with MeHg poisoning, but did receive penicillamine for suspected toxicity. CF was seen and examined at the Departments of Neurological Medicine and Pediatrics at Niigata University Medical School in September 1965, but no specific diagnosis was made.

At 10 months of age CF was admitted to the Department of Pediatrics for a more comprehensive evaluation. At that time she could not sit alone, had poor head control and could barely vocalize. Her vision appeared normal and there was no evidence of a visual field constriction. She would try to reach for objects. Her hearing was normal. She had extensor Babinski reflexes bilaterally. Pneumoencephalography disclosed the presence of atrophy in the frontal and occipital lobes and the cerebellum. During the hospitalisation she was given penicillamine and the quantity of mercury excreted in her urine was 697-1272 µg/L. Although she had elevated hair and urine mercury values, her illness was diagnosed as cerebral palsy. When she was 11 months of age in April 1966 she could recognize her mother. By age 18 months, she would sometimes play with toys. At 20 months of age she was examined and found to have a normal height and weight, but her head was large and the occipital region flat compared with normal children. At that evaluation, her face was expressionless and she drooled continually. She was able to follow a moving object with her eyes, but with coarse saccadic eye movements. She could hear sounds and vocalize, but could not speak. She would smile in response to hearing her name called. Involuntary movements of her body would occur occasionally in response to loud noises. She had difficulty holding her head stable and there was hypotonia of her trunk. She was unable to change her posture in bed or to crawl on the floor. When suspended upright, her upper body

was bent forward, her legs were crossed and her feet were plantar flexed. She tended to keep her hands tightly fistled, but could open them and occasionally grasp a toy. On opening her hands, the fingers would overextend and she had dystonic postures. She had ataxia, an intention tremor and occasional athetotic movements. Her deep tendon reflexes were normal bilaterally. She had a persistent suck reflex and extensor plantar responses. She was sent for rehabilitation to the Hamagumi Gakuen, but her findings did not change.

Between 2 and 3 years of age, CF started standing by holding objects around her. By around age 3 years she could understand conversations and could pronounce such sounds as "a", "un" and "ai". She also started toilet training, began to hold her head in the upright position, and showed more interest in her surroundings. With assistance, she could walk a little and was able to eat her meals using a spoon. By the age of 5½ years, her head circumference was 51.5 cm, but she still had flattening of the occipital region. Her face was without emotion, but gradually over several years her countenance became more changeable. She was able to distinguish each family member, could use a few words, and was able to express her desires. Her hearing was normal and she could speak a few words, but had difficulties with sentence construction. She could count up to six, show her age with her fingers, play with toys, and showed an interest in picture books. She could still not pile up blocks in an orderly way. She would watch TV and could remember her favourite programs. Her eyes showed normal pupils, but she still had coarse saccadic eye movements. There was no constriction of the visual fields. Her tongue movements were fairly skilful and she had no difficulty swallowing. She still had difficulty keeping her head in the upright position and her trunk was hypotonic, but her extremities had increased tone. There were involuntary movements resembling athetosis. She tried to grasp toys not with her fingers, but with her whole hand. She was unable to draw circles. She could walk with support. While walking, her heels did not touch the floor. Her ankle jerks were hyperactive and she had pathologic reflexes bilaterally, but the primitive reflexes had disappeared. She continued to drool. No abnormalities in sensation were observed.

Repeat medical examinations of CF's mother between 1967 and 1970 were considered within normal limits. In 1970 she reported muscle twitching and stiffness, tiredness, tinnitus and blurred vision. On examination in 1975 she had poor coordination, abnormalities on cerebellar testing (adiadokokinesis and abnormal heel-shin testing) and distal sensory loss in the extremities. She was never formally diagnosed with Minamata Disease.

During the presentation of the legal case for CF, Dr. Saito and Dr. Harada testified (13). They considered CF a case of congenital Minamata disease for several reasons. First, there was exposure in that the mother consumed large amounts of fish contaminated with methyl mercury during her pregnancy. Second, the mercury level measured in both mother's and child's hair was significantly elevated, as was the urine mercury after a penicillamine challenge. Third, the developing brain was known to be especially sensitive to MeHg exposure. In addition, the clinical findings were similar to those of other patients diagnosed with congenital Minamata disease in that she had intellectual and speech impairment, pyramidal and extrapyramidal signs, cerebellar signs, strabismus and persistence of primitive reflexes. The court found in favour of CF and officially declared her a victim in 1970 making her eligible for compensation.

She is now 39 years of age and lives at home with her parents. She had surgery to the tendons of her feet and hands, after which her heels were able to touch the ground when she walked and she was able to grasp with a little more ease than before. Although walking became a little easier, she still can't walk without support. She has choreoathetosis. She is able to express herself in writing, but does not speak. She enjoys cooking and shopping. She tires easily, but travels about Niigata alone in an electric cart. She is now an advocate for handicapped citizens and organizes activities for them.

### Case 2

FW was born on 8 April 1965 [Case 2 in group B in the paper by Saito et al in this issue (12)]. Her mother's pregnancy and her birth were normal. Her father's family business was fishing on the Agano River and both her parents ate large quantities of fish. In June 1965 when she was 2 months old, hair mercury concentrations in the family were measured using the dithizone method. Her father's hair mercury level was 116 ppm, her mother's 35 ppm, and hers 63 ppm. She appeared to be a normal baby, but when the elevated hair mercury was found she was given penicillamine and 2-mercaptopyrionylglycine for 2-3 weeks. She walked at 20 months of age and spoke her first words at 2½ years. She was toilet trained between 3 and 4 years of age. In school she had a poor academic record. She was not as athletic as her peers and tended to tire more easily. Sometimes she had muscle cramps and twitching. She had frequent colds and often complained of headaches and ringing in her ears. In the second or third grade she began to have vertigo and was unable to play on swings. She complained of motion sickness riding in a car. During elementary school she noted numbness in her limbs and poor sensation in her fingers. She did not like manual work or art. She menstruated at age 12 years and was married at age 23. She subsequently had two children who are normal.

In 1967 her father who was then 33 years of age complained of muscle cramps, numbness of the limbs, and dizziness. He was evaluated for Minamata disease, but never officially confirmed.

When FW was examined in February 1996 at the age of 31 years, there was no evidence of impaired cognition or of a movement disorder. She was found to have a slight decrease in her peripheral vision by confrontation testing. She also had a mild disturbance in her equilibrium on tandem gait and difficulty standing on one foot with her eyes closed. There was decreased sensation around the mouth, on the lower abdomen, on the buttocks, and on the distal extremities. She has not been officially recognised as having Minamata disease, but her exposure history and clinical findings are suggestive of that diagnosis.

### Outside Japan

No patients with confirmed congenital MeHg poisoning from fish consumption have been reported outside of Japan. There have been reports of possible poisoning from Canada, China and the Amazon (14-18). However, they have not been well documented in the peer reviewed literature. The last known exposure in Japan from consumption of fish is believed to have occurred in 1965. There are documented cases of congenital MeHg poisoning from sources other than fish that have been reported from Sweden, Iraq and the United States. In 1952 a Swedish family consumed porridge prepared from flour that had been treated with an alkyl mercury compound

(19). The family had a boy aged 16 months at the time they were eating the contaminated porridge. That boy exhibited signs of cerebral palsy and mental retardation. The mother did not show any physical or mental abnormalities. Shortly after consuming the porridge she gave birth to a baby girl. As that child grew, she also had mental retardation, and neurological signs similar to those of her brother. That case was the first congenital MeHg poisoning reported. The case history suggested that organic mercury might be transferred across the placenta and could seriously affect the fetus. Cases of congenital organic mercury poisoning were reported from Iraq after consumption of MeHg treated seed grain (20-21). In the United States there is one report of a family who consumed pork after the animal had been fed MeHg treated grain (22). All of the reported patients have had serious neurological disability and mercury exposures substantially above those achieved by fish consumption.

## Discussion

The two Japanese cases described above illustrate the danger of prenatal MeHg exposure from consumption of fish polluted by methyl mercury from industrial contamination. The case of CF is of special interest because she is the only case of prenatal poisoning from fish consumption for which the exposure near the time of birth is actually known. Her mother's hair mercury level was 293 ppm measured one month after her birth. At Minamata no mercury levels were measured during pregnancy or near the time of birth. When Dr. Harada first described fetal or congenital MeHg poisoning (5), the youngest child had been over a year old at first evaluation.

Our second case (FW) is of interest because her exposure to MeHg was measured at 63 ppm using the dithizone method when she was 2 months old. Despite this, she did not have the severe neurological damage seen in all previously reported patients. Following the Minamata exposure, there were statements about the high rate of cerebral palsy in the area, but these were not well documented. No other patients with well documented exposures and less severe symptoms have previously been reported, but it is possible that such patients exist.

## Summary

The history of pollution at Minamata and Niigata and these two case reports illustrate the serious risks of MeHg exposure and why our society must protect its citizens and the environment from pollution. The case history of CF is especially valuable since she is the only subject with congenital Minamata disease for whom exposure was measured near the time of birth.

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