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Special Feature

Intrauterine Methylmercury Poisoning - Congenital Minamata Disease

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In May 1955, many cases of neurological disease of unknown cause were found in the Minamata region. By the summer 1959, it was revealed that the mysterious disease was a methylmercury (MeHg) poisoning caused by ingestion of MeHg-contaminated fish and shellfish, and that a chemical plant in Minamata City had long been discharging the polluting effluent. Methylmercury poisoning caused by ingestion of contaminated fish and shellfish due to environmental deterioration was later defined particularly as Minamata disease. Most of the known MeHg intoxication at that time was either occupational or accidental. Discovery of Minamata disease also revealed that many children born at the same place and the same time of Minamata disease incidence were diagnosed with cerebral palsy. Based on the pattern of incidence, the palsy was suspected of its connection with Minamata disease from the beginning. Nevertheless, medical science at that time did not have enough proof that a toxicant could pass through placenta and severely harm the fetus. Besides, there were other factors that prevented us from reaching definitive conclusion, such as very mild symptoms of mothers, delay indiscovering the disease itself, total lack of birth data, no unique symptoms when compared to general cerebral palsy, and lack of successful animal test results.

Although each showed symptoms similar to cerebral palsy in general, every one of the patients exhibited identical symptoms. For this reason, I deduced that the cause must be uniform. In addition, epidemiological studies found that its outbreak was completely coincided with Minamata disease both in timing and location. The disease was also characterized in that patients' family members developed Minamata disease, their mothers consumed a large amount of fish and shellfish from Minamata Bay during pregnancy, and the mothers also exhibited mild manifestation of Minamata disease. Based on these findings, I concluded that the disease was a prenatal methylmercury poisoning, although medical academia dismissed it for lack of evidence. Incidentally, three-year- and six-year-old girls successively died in August 1961 and September 1962. After performing autopsy, Prof. Tadao Takeuchi of Kumamoto University diagnosed as "methylmercury intoxication developed during fetal life". In combination with my study ("common symptoms indicated a single cause"), all the seven patients were officially certified with congenital Minamata disease in December 1962. The world's first case of transplacental toxin exposure was confirmed, where the substance could gravely impair a fetus without seriously harming the mother.

Incidence Rate and Childbirth Process

In the three districts with mostfrequent incidence of Minamata disease (Yudo, Modo, and Tsukinoura), 188 babies were born between 1955 and 1958. There were 13 congenital Minamata disease patients in these areas, which makes the incidence rate as 6.9%. With the additional four incomplete patients found after health examination of all the school children in the districts, the rate rose to 9.0%. Compared to the nationwide rate of cerebral palsy (0.2%) in Japan at that time, the rate in Minamata was abnormally high. Subsequently, congenital Minamata disease patients were found one after

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another. They were concentrated in fishing hamlets around Shiranui Sea area where incidence of Minamata disease was confirmed. I have so far identified 66 patients. The incidence was also concentrated between 1952 and 1963, which means that development of congenital intoxication coincided time-wise and location-wise with Minamata disease.

Mothers consumed a large quantity of fish and shellfish of Shiranui Sea during pregnancy. Some newborn babies were breast-fed, and others were bottle- or mixed-fed. There were only two cases of troubles during childbirth; all the others displayed no abnormality at labor/delivery. The examined mothers generally showed mild symptoms. That said, 100% of them experienced loss of sensation, and 79% and 57% were observed withminor ataxia and constriction of visual field, respectively. The 1962 survey identified that 64% had at least one typical Minamata disease patient in their family. Subsequent family investigation found that all of them had family members with mild to severe Minamata disease.

Fishers around this coast eat a large amountof fish and shellfish all year around, especially in summer between May and July. In contrast, the seafood ingestionis relatively low between December and March. Babies with congenital Minamata disease were most frequently born in September and October. Judging from the duration of pregnancy, bulk consumption of fish and shellfish between sixth and eighth months of pregnancy highly induced congenital Minamata disease. As for the gender, there are 36 male and 30 female patients. Around 1956 at the height of contamination, more female patients were born, while the number of male birth were low. During the periods when the contamination was somewhat eased (pre-1953 and post-1960), more male than female patients were born. Gathering from these data, we can hypothesize that male fetus are more susceptible to methylmercury than female.

Clinical Manifestation and Its Course

A severe case of congenital Minamata disease would be clinically diagnosed as cerebral infantile palsy. On the other hand, there are some unique characteristics to the former; no laterality of symptoms was manifested, and no abnormality-inducing factors were observed during childbirth. In the early stage, the patients showed common symptoms with an identical pathological image. Specifically, in 1962, 100% of patients had mental disability, dysarthria, incordination, deformed limbs, primitive reflex, hypersalivation, and nutritional disorder, and other common symptoms such as chorea and athetosis (95%), paroxysms (82%), strabismus (77%) and pathological reflex (75%) were observed. All of these helped illustrate the same pathological image. Among those in severe conditions, 13 patients have died. Six were autopsied, and all exhibited the common pathological findings with a high level of residual methylmercury. Subsequently, the surviving patients showed some degree of easing symptoms (functional development). The 1990 research of 51 cases found improvement in paroxysms (29%), hypersalivation (39%), primitive reflex (41%), deformed limbs (41%), and incordination (69%). Meanwhile, dysarthria and strabismusremained, whereas mental disorder was more progressed than it seemed, with 44% of severe cases.

Symptoms, as seen above, were improved at some point. However, after turning 40 years old, the patients exhibited apparent deterioration of their disease. Subjective symptoms, such as headache, dizziness, daze, insomnia, frustration, and tinnitus, had manifested and exacerbated. In particular, arthralgia and lumbago had noticeably worsened. Not only the subjective symptoms but also the motor function was obviously degraded. Among those who could walk even with difficulty, for instance, five patients had evidently lost their mobility. The cause may be simply aging or relapse of symptoms as seen in poliomyelitis; we must rely on the future studies for elucidation. At present, only seven patients are still hospitalized, and others live at home while regularly going to hospital and/or rehabilitation centers. Three of them earned income without relying on the rehabilitation center, although they took a leave of absence after reaching 40 years old. Three work as fishing assistant, and one is engaged in acupuncture/moxibustion therapy; all of them barely support themselves with family assistance.

Pathological Findings

The pathological findings of Minamata disease are highly distinctive, which are known as Hunter-Russel syndrome. Specifically, lobus occipitalis, precentral/postcentralgyrus, and transverse temporal gyrus of the cerebral cortex are severely damaged in a localized and characteristic manner. Furthermore, the cerebellum shows granular cell-type cerebellar atrophy. Pathological findings of the congenital Minamata disease are basically the same as those of the acquired Minamata disease. In addition to these, the former exhibited general hypoplasia and dysgenesis (developmental disorder) of both cerebral and cerebellar cortexes. To be more specific, abnormality of the cytoarchitecture, remaining matrix cells, intramedullary preservation of the nerve cell, corpus callosum, and dysmyelination of the pyramidal tracts, as well as hypoplasia of the granular cell layerand empty granular cells in the cerebellum, were observed. Takeuchi reported the findings that showed ateliosis attributed to the damages during the later fetal life and distinctive disorder caused by methylmercury poisoning. This was the first brain profile of the prenatal methylmercury poisoning. A successful animal test using the radioisotope (Hg203) confirmed the transplacental passage of methylmercury, which damaged the fetus through its accumulation in the brain (Shiraki *et al.*). According to the experiment, 1.39% and 1.16% of the methylmercury administered to a mother rat was transferred to the fetus, and a newborn monkey by birth had accumulated methylmercury 2.25 times more than the mother. Another experiment also confirmed the MeHg transfer to a child through breast milk.

Abortion, Stillbirth, and Congenital Anomaly

Methylmercury is believed to cause primarily fetopathy, but not embryopathy. Empirically, there are few cases of embryopathy (congenital anomaly). One of the reasons is considered as its induction of miscarriage and stillbirth. The 1977 survey revealed that, among 272 pregnancies of total 89 women in the high Minamata disease incidence areas, there were 32 miscarriages, nine stillbirths, and four neonatal deaths within one week. The stillbirth/abortion rate was 15.0%. According to the investigation of other contaminated areas, the stillbirth/abortion rate, which was 4.2% in 1945, rose to remain 30+% during the most polluted period, and marked 42.9% in 1963. Another study reported 26.0% during the period with high contamination. It is evident that the heavily contaminated period witnessed high rates of miscarriage and stillbirth.

Another reason is the possibility where the cases with birth defects were excluded from diagnosis of congenital Minamata disease from the beginning. In fact, congenital Minamata disease patients were observed with anomalies such as polydactyl, high palate, defective external acoustic meatus, microcornea, and protrusion of the coccyx, whereas microcephalyus, polydactyl, an undescended testis, enlarged colon, and other malformations occurred in some cases that were not diagnosed as congenital Minamata disease. One of the latter cases recorded 2.42-ppm methylmercury in the umbilical cord. Besides, there were babies with Down syndrome and Laurence-Moon-Biedl syndromeborn by the mothers diagnosed with Minamata disease. Based on these data, it is inconclusive to deny the teratogenic potential of methylmercury, yet it is unlikely to be a major symptom.

Mercury Level in Umbilical Cord

In early days when the cause of Minamata disease was unknown, the mercury levels were never measured. In addition, identification of congenital Minamata disease took time, which all made diagnosis of congenital Minamata disease quite difficult. For instance, mercury analysis started as late as in 1960, and measurement was limited to only a fraction of residents. Furthermore, methylmercury was analyzed only after 1966. For these reasons, diagnosis of the congenital poisoning was delayed. Fortunately enough, however, there is a custom in Japan to keep part of the umbilical cord of a newborn baby. I realized this practice in 1974, and collected the preserved umbilical cords in the contaminated region to analyze the methylmercury concentration. The preserved umbilical cord marked an elevated level of methylmercury, the highest of which was 5.28 ppm. For example, the MeHg

concentration in the umbilical cords of Tokyo residents was somewhere between 0.1 and 0.2 ppm. Those of the fishers in Jakarta Bay showed 0.037 to 0.089 ppm, and those of the residents near a gold mine registered 0.08 ppm, both relatively low compared to the Minamata cases. Since the preserved umbilical cord contains blood, what we had measured was more precisely a cord blood. In any way, it is understood that these figures illustrated a part of a picture of the mercury pollution in mothers and babies at childbirth.

As for the majority of the congenital Minamata disease patients, the preserved umbilical cords marked over 0.5 ppm of methylmercury. That said, the MeHg levels do not necessarily correspond to the clinical conditions. Some infantile Minamata disease cases showed a high level of concentration. With continuous contamination, we can see that the differentiation between congenital and infantile Minamata diseases is more relative than absolute. It should be noted that the patients with unnoticeable neurological symptoms (mainly mental disorder, autism, and behavioral disturbance), who have not been diagnosed as congenital Minamata disease, also had a high concentration of methylmercury. Due to these, it appears necessary to review the pathological image of congenital Minamata disease. The MeHg level in the umbilical cords corresponded well with the acetaldehyde production of Chisso and its estimated volume of mercury discharge. For other chemical pollutants including dioxin and PCB, the preserved umbilical cord can provide an opportunity to retrace and analyze the past levels of contamination. In this sense, application of umbilical cord analysis is expected to expand in the future.

Prenatal Effect of Methylmercury

All the congenital Minamata disease cases observed in Minamata were in seriousconditions. Similar cases were reported from other areas, such as Niigata (one), Sweden (one), U.S. (one), Iraq (five) and Russia (three). These are, again, only severe cases as seen in Minamata. The Niigata report revealed that the mercury level of the mother's hair was 293 ppm at the time of childbirth, and that of the baby at the sixth month was 77 ppm. In the U.S. case, the blood mercury level of the mothersix months after childbirth recorded 2,910 ppb. The Iraqi study reported that the blood mercury contents of the mothers at delivery were 180 to 2.390 ppb, and their children (with intrauterine methylmercury poisoning) had the blood mercury levels between 564 and 4,220 ppb. Since these reports only covered the most severe cases, it is assumable that there are more incidences of cerebral dysfunction at various degrees surrounding these serious cases.

Meanwhile, the International Programme on Chemical Safety (IPCS) published a draft report in February 1985, which questioned the safety in applying the same provisional mercury tolerance level (50 ppm in hair sample) to the fetus. IPCS specifically referred to three studies. The first paper covered the agrochemical mercury pollution in Iraq, which reported that five mothers whose hair mercury levels were between 165 ppm and 320 during pregnancy all gave birth to babies (five in total) with fetal methylmercury poisoning. Follow-up survey on other mothers and babies revealed that an intoxication effect was observed in children born by the mothers whose hair mercury level was 14 to 18 ppm during pregnancy. The second report was from New Zealand on a fish-eating tribe; the hair mercury levels of pregnant women and their children's symptoms were tracked over four to six years. Based on the findings, the study concluded that the mother's hair mercury limit was 13-15 ppm to exert psychological, linguistic, behavioral, and intellectual influence on the child, and reported that the highest marked 26 ppm.

Furthermore, a Canadian survey found that children had developed dysmyotonia when mother's hair mercury level was between 13.00 ppm and 23.9 ppm. Subsequently, a seven-year follow-up study was conducted on inhabitants of Faroe Islands in Denmark, whose diet includes high intake of whale meat. The researchers concluded the minimum hair mercury concentration that could cause attention deficiency, visuospatial disorder, language disability, memory impairment, and other brain dysfunction to be 15 ppm. As seen in these reports, the safety standard regarding prenatal mercury exposure was being reviewed. Consequently, many countries including Japan now advise pregnant women to

limit their fish intake. In setting the chemical safety standard, it is important to remember that the tolerable exposure for pregnant women and their unborn babies is different from that of the general public. At the same time, some urge the limit of seafood intake for pregnant women, while others stress the important nutritional values of fish and shellfish.

In Minamata, at least 200,000 people were heavily exposed to mercury pollution. In the past, we had excessively limited the scope of Minamata disease to only the most severe cases. As a result, submerged symptoms have long been neglected. This is particularly true with the congenital Minamata disease. In fact, surveys have been finding hidden impairment in seemingly inconspicuous residents of Minamata. In such cases, the mercury level ofthe preserved umbilical cord can provide an important lead. While the existing cases of congenital Minamata disease can be described as cerebral palsy type, there are other newly found patients with a high cord mercury level who were diagnosed with mental disability, autism, dementia, behavioral anomaly, or other cerebral dysfunctions. In the future, it is expected that the prenatal/infantile effect of trace mercury exposure will raise a worldwide concern.