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Apallic Syndrome in Chronic Mercury Poisoning

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Abstract. This report includes five cases afflicted by chronic mercury poisoning which was observed in Iraq in 1972. All five cases showed the symptomatology of a severe cerebral damage combined with peripheral nerve lesion. The clinical picture reveals an apallic syndrome or a prestage ensuring in the full-blown picture. The combination of CNS lesions with polyneuropathy is typical of mercury poisoning with failure of all brain functions and the appearance of brain stem automatism, combined with severe muscular atrophy. When such conditions are established the remission seems to be impossible.

The historical as well as the clinical and morphological facts of the Minamata disease is reviewed. The different stages of chronic mercury poisoning in Iraq are described.

Introduction

At Minamata Bay in southwestern Kyushu, Japan, in 1953, sporadic cases of curious neurological disorders were observed. In the following few years the disease took the form of an epidemic wave. *Takeuchi* (1958) in his first report mentioned that the neurological disorders were due to a toxic encephalopathy without a primary inflammation. In later epidemiological studies it was found that all the patients affected by this unknown disease had eaten fish, especially shellfish, contaminated since 1952 with effluent of a factory producing acetic acid, aldehyde, and vinyl chloride.

In 1958, *Takeuchi* pointed out that the pathological features of this neurological disease were very similar to an organic mercurial poisoning as described by *Hunter and Russel* (1954). A high mercurial content found in the organs of autopsy cases confirmed the suspicion.

The pathological changes in sick animals living on fish from Minamata Bay were similar to those found in the human cases (*Kitamura et al.*, 1960).

From 1953 to 1960, 59 adults, 30 children and 22 infants affected during intrauerine life by the so-called Minamata disease have been registered in Japan. 41 of these died (29 adults,

10 children and 2 infants with a connatal affection). As cardinal symptom trias was described: cerebellar ataxia, dysarthria and constriction of visual field (Hunter-Russel's syndrome by *Pentschew,* 1958). *Takeuchi* (1968) suggested that other signs had to be added. He found the corresponding pathological changes in different parts of the brain in 23 autopsy cases from 1956 to 1965.

In 1972, in Iraq, a number of patients with cerebral, spinal as well as peripheral symptoms were observed. The chronic mercury poisoning was caused by eating wheat preserved with a mercurial compound.

Case Reports

In 1972, five cases of a severe chronic mercury poisoning were observed and examined neuropsychiatrically in the Baghdad University Hospital. In one of them postmortal chemical findings were available. Their case histories are described here.

Case 1

K.H. Jamal, female, 30-year-old farmer's wife. Pregnant for 6 months. During 4 months the family (7 persons) had been eating 100 kg of wheat treated with a mercurial compound. After 2 months there was appearance of fever, dizziness, unsteady gait and speech difficulties. In the next 2 weeks progression of the symptoms followed by somnolence, stupor and finally by a comatous state. At the same time, gradually decreasing motor activity, deterioration of general condition. 6 weeks before admission the patient became bedridden and had to be fed. After hospitalization a mercury poisoning was diagnosed and the specific treatment (BAL) was started immediately, but without effect.

Neurological findings (April 12, 1972). Coma vigile with alternating periods of wakefulness and sleep; no reactions to surroundings and no emotional reactions; undirected and sluggish mass movements of the extremities and the head in stereotypes in response to painful stimuli, sometimes associated with a stretch tendency in the legs. Divergent eye position, tendency to convergence and to skew deviation (right eye upwards), bilateral ptosis, doll head phenomenon (oculocephalic reflex) in all directions (not fully developed); pupils of medium size, diminished reaction to light, ciliospinal reflex positive. Temporal disc paleness, hypertonia of the masseter muscle, masseter reflex slightly increased; no atrophy or fasciculation in the tongue; diminished excursion of the soft palate,

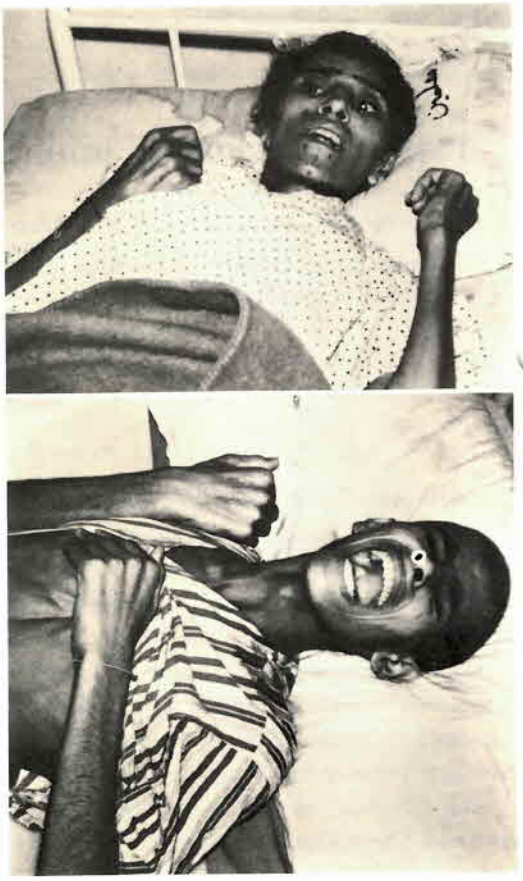

Fig. 1. K.H. Jamal, female, 30 years, apallic syndrome (full stage) chronic mercury poisoning, coma vigile, amimia, open mouth, divergent eye position, fist position, flexed position of the arms, wasting of the hand muscles.

Fig. 2. Patient A.A. Ali, male, 15 years, apallic syndrome (prestage) chronic mercury poisoning. Flexed upper limbs with fist position, generalized muscle wasting.

diminished gag reflex, amimia. Flexed arms, stretched legs, fist position with covered thumb (fig. 1), plantar flexion of the feet, ankylosis of the joints; hypertonus of all skeletal muscles with spasticity and cogwheel phenomenon (rigidospasticity); increased tendon jerks, Hoffmann-Babinski phenomenon positive, Rossolimo group negative. Generalized muscle wasting especially of the hands and of the peroneal muscles. Hyposensitivity for all qualitites in the distal part of the extremities. Marked primitive motor reflexes such as phasic and tonic grasp reflexes, tactile and optic oral reflexes, snout reflex, various types of mental reflexes, asymmetric tonic neck reflex and chewing and swallowing automatism.

Three weeks after admission the patient died due to renal failure. No change in the symptomatology was observed.

Case 2

A.A. Ali, male, 15-year-old farm-worker. 9 weeks before onset of neurological symptoms the family started eating bread made from wheat treated with a mercurial compound. Ten persons ate 100 kg in 2 months. At first, the patient complained of generalized numbness, with difficulties in walking and with visual disturbances. A skin rash appeared. The patient's condition deteriorated very rapidly in the following weeks. A comatous state developed, artificial feeding was necessary. The patient was hospitalized in the University Clinic 7 weeks after onset of the first complaints. A mercury poisoning was diagnosed and a treatment with BAL started.

Neurological findings (April 14, 1972). Vigilance highly diminished, alternation of sleep and wakefulness disturbed, however, influenced by day-night regulation. Optic fixation possible, optic following only to a small degree, threat reflex slightly positive. Spontaneous rhythmic cat cry with mimic reaction increased by painful stimuli (fig. 2). Pupils enlarged with diminished light reaction, ciliospinal reflex positive: divergent position of the eyes with periods of slow horizontal eye movements, deviating to the right, while the head deviated to the left, positive doll head phenomenon (oculocephalic reflex). Temporal half of the disc pale in both fundi. Increased masseter reflex, diminished gag reflex. Atrophy of temporal and masseter muscles; hypersalivation, seborrhea and amimia. Flexed upper limbs with fist tendency, stretched lower limbs, increase of this position by any stimuli; muscle tonus slightly increased (rigidospasticity); biceps jerk increased on the left, absent on the right, triceps reflex diminished bilaterally, knee jerks increased bilaterally, ankle clonus bilaterally; Hoffmann reflex positive, Babinski phenomenon with escape reflex, Rossolimo reflex bilaterally positive. Muscle wasting, more marked on the distal extremities. Pain sensation in the distal parts of the limbs diminished. Abdominal skin reflexes absent, deep abdominal reflex present. Primitive reflexes such as phasic grasp reflex (slight), tonic grasp reflex (moderate–severe), palmomental reflex (slight), snout reflex, tactile oral reflex present. Symmetrical tonic and asymmetrical tonic neck reflex absent. There was a tendency to grasp all objects in the nearest surroundings and to bring them to the mouth, as well as masturbation activities.

The neurological condition deteriorated within 10 days into the direct prephase of the apallic syndrome showing optic fixation and following as well as primitive emotional reactions. The patient died 12 days after admission from acute renal failure. 10 h before death the patient developed symptoms of an acute midbrain syndrome, which was followed by a bulbar brain symptomatology.

The mercury blood level of this patient was 32,000 ng/ml (10th day after admission). The postmortal findings of mercury content in different parts of the brain (Pathological Institute, University of Baghdad) were: frontal lobe, 18.32 ng/g; parietal lobe, 18.7 ng/g; calcarine fissure, 7.55 ng/g; basal ganglia, 18.95 ng/g; cerebellum, 11.1 ng/g; optic nerve, 5 ng/g; medulla, 6.3 ng/g; sciatic nerve, 3.84 ng/g; synaptic chain, 1.87 ng/g.

Case 3

M.A. Ali, male, 17-year-old farm-worker, brother of A.A. Ali (case 2). Same history as case 2 but with slower development of the symptomatology than his brother, and at the same time numbness was remarked, beginning in the feet distally, followed by difficulties in walking (weakness and ataxia). The patient was hospitalized in the University Clinic on the same day as his brother.

Neurological findings (April 14, 1972). Vigilance highly diminished, however, no coma vigile, threat reaction positive, optic fixation present, no optic following; sleep-wake disturbance, partially, daytime regulation acting, delayed reactions to painful stimuli, responsed with mass and stereotyped movements combined with primitive emotional reactions. Slight spontaneous motor sterotypes. Divergent position of

the eyes with short periods of convergence, slight ptosis bilaterally. Oculocephalic reflex positive; medium-sized pupils; ciliospinal reflex on the right side positive, while absent on left. Both optic discs pale. Flexed position of the upper limbs, stretched legs, fist tendency both sides; increased muscle tonus (rigidospasticity); knee jerk diminished, ankle jerk subclonic; Hoffmann reflex negative, Babinski phenomenon with escape reflex. Muscle atrophy more marked distally, especially in the hands. Hyposensitivity upper and lower extremities both sides distally. Primitive reflexes present as snout reflex, tactile oral reflex, sucking, chewing and swallowing automatism, slight glabellar reflex; no tonic neck reflexes.

Within 3 weeks the patient developed the full stage of an apallic syndrome. 2 weeks later he died of renal failure, without signs of an acute brain stem symptomatology. The patient had undergone a specific therapy including BAL and hypercaloric nutrition.

Case 4

J. Jabor, female, 14-year-old farm-worker. Four members of the family consumed within a period of 3 months about 50 kg of wheat treated with a mercury compound. Three of them became affected while one (the grandfather) remained in good health. The symptoms appeared 1 month after that 3-month period, starting with numbness in the extremities and around the mouth, general weakness followed by ataxia, dysarthria and blurred vision. Within 20 days the patient became bedridden and comatous.

Neurological findings (April 20, 1972). Coma vigile, periodic alternation of sleep and wakefulness, no optic fixation and following, rhythmic cat cry with stretching tendency of the body and the extremities, exaggerated by painful stimuli. Normal fundi. Slight ptosis bilaterally, divergent eye position, no doll head phenomenon. Pupils contracted, diminished light reaction, positive ciliospinal reflex. Gag reflex diminished, jaw jerk increased. Upper extremities flexed, lowers stretched, fist position on both sides; increased muscle tonus more in the flexors of the arms and extensors of the legs; increased tendon jerks. Pyramidal tract signs upper and lower extremities, absent abdominal skin reflexes. Slight muscle atrophy in upper and lower extremities in the distal parts of the extremities. Pin prick sensations. Incontinence. Primitive reflexes such as chewing and swallowing automatism, tactile oral reflex, snout reflex, slight tonic neck reflexes.

In the next 6 weeks no change of symptoms was observed. The patient died 10 weeks after admission in acute state of pneumonia with heart failure.

Case 5

S. Jabor, female, 18-year-old farm-worker, sister of case 4. Same history as her sister. First symptoms appeared at the same time and with the same complaints.

Neurological findings (April 20, 1972). Coma vigile, alternating sleep and wakeful periods, no optic fixation; painful stimuli followed by mass movements of the extremities, rhythmic cat cry with stretching tendency of the extremities. Slight ptosis bilaterally, divergent eye position, contracted pupils with diminished light reaction, slight positive ciliospinal reflex; increased jaw jerk, diminished gag reflex. Fundi normal. Extended limbs, no fist position; muscle tonus diminished in upper limbs, increased in lower limbs; increased tendon jerks, slight pyramidal signs, no abdominal reflexes. Slight muscle distally atrophy upper and lower limbs. Pin prick diminished distal extremities. Primitive reflexes such as chewing and swallowing automatism, tactile oral reflex, glabellar reflex, snout reflex, tonic grasp reflex, slight tonic-neck reflexes.

In the next 6 weeks no change in the symptomatology was observed. The patient died 8 weeks after admission of renal failure. The therapy including BAL started immediately after hospitalization.

In all of the five cases described a chronic mercury poisoning with severe cerebral and peripheral nerve symptoms appeared after a different time of consuming mercury-prepared wheat (1–3 months). The details of the clinical picture were not well followed, but it seems that in all cases the peripheral symptomatology was the initial complaint, followed by cerebellar symptoms. Later, there were disturbances of the higher brain functions, at the same time spastic and Parkinson symptoms as well as optic nerve lesion with constriction of the visual field. Finally, failures of all higher brain functions developed and a chronic decortecate state was observed.

Cases 1, 4 and 5 showed the full state of an apallic syndrome at the first examination, cases 2 and 3 developed during their hospitalization the symptomatology of an apallic syndrome. The first examination of these two cases showed preapallic symptoms, case 3 the stage of optic fixation and primitive

emotional reactions, case 2 the Klüver-Bucy phase. Four cases died in the full stage of an apallic syndrome. Case 2 developed the direct prephase of the apallic syndrome and died in an acute brain stem syndrome (bulbar brain syndrome according to *Gerstenbrand and Lücking*, 1970), due to an acute uremic coma. The postmortem findings are not available.

Discussion

The principal types of mercury poisoning are the acute and the chronic types. Acute poisoning can occur either through ingestion of mercuric salts or through inhalation of a high concentration of mercury vapor, causing after 1 or 2 days a metallic taste, stomatitis, salivation, severe abdominal pain, vomiting and blood diarrhea. Neurological symptoms such as dizziness, clumsiness, slurred speech and in some cases epileptic seizures appear. Death is from kidney damage in uremic coma.

Chronic poisoning can occur either through injection of organic mercurial compound or ingestion of insoluble or poorly dissociated mercuric salts over a prolonged period. Other possibilities are inhalation of low concentrations of mercury vapor or dust and skin contact with mercury compounds for a long time. The chronic poisoning causes mercurialism with variable clinical findings. Early signs of mercurialism are urticaria, progressing to weeping dermatitis, stomatitis with salivation, loosening of the teeth, blue line on the gums, diarrhea, anemia, leukopenia, symptoms of dysfunction of the liver and of renal damage progressing to acute renal failure with anuria. In addition to these initial symptoms, neuropsychiatric symptoms with headache, pains and weakness in the arms and legs, tremor, depression and emotional lability ensue. The neuropsychiatric symptomatology gradually deteriorates with the development of paresis, bulbar symptoms, ataxia, increased tremor, visual and hearing disturbance, convulsions, hallucinations, mental deterioration with symptoms of a diffuse brain damage. As mentioned before, *Takeuchi and Morikawa* (1960) described the characteristic trias as cerebellar ataxia, dysarthria, constriction of visual field in the chronic mercurial poisoning. Later, *Takeuchi* (1968) classified the Minamata disease in a latent type (subclinical), incomplete (partial masked) type and the complete type. From the latter the symptomatology can progress to the apallic syndrome and death (fig. 3).

The mercury poisoning cases in Iraq according to their neurological appearance can be classified into four groups: mild neurological symptomatology, less severe neurological symptomatology, severe neurological symptomatology and apallic syndrome (fig. 4). In all four groups different degrees of lesion of the skin, gastrointestinal tract, as well as disturbance in the liver and kidney functions are observed.

The first group is characterized by paresthesiae and mild paresis as symptoms of polyneuropathy, accompanied by mild symptoms of a lesion of posterior tract and cerebellar signs together with a bulbar paralytic symptom as well as the beginning of an organic psychosyndrome with depressive signs.

In the second group the above-mentioned symptomatology is well established in addition with spastic symptoms, mild extrapyramidal symptoms as a combination of Parkinson symptoms with chorea-athetotic hyperkinesia and optic nerve symptoms.

In the third group patients show severe neurological symptomatology in form of generalized cerebral deterioration with decrease of vigilance and of emotional reactions, failure of the higher brain functions specially expressive and perceptive speech disturbances, constriction of the visual field sometimes to complete

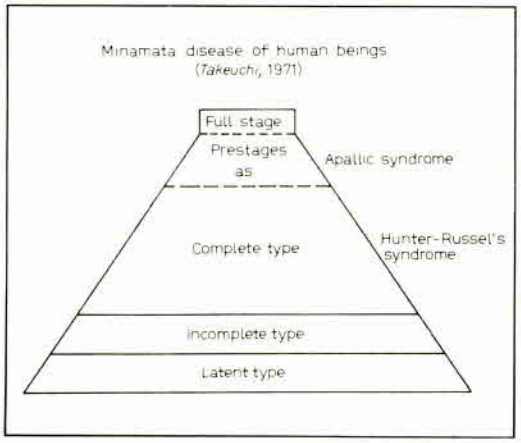

Fig. 3. Schema of the different types of Minamata disease (modified according to *Takeuchi,* 1971).

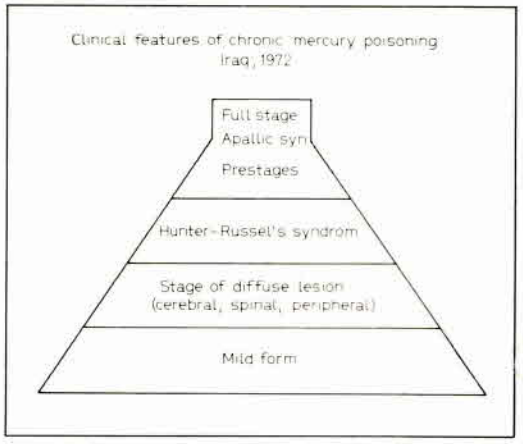

Fig. 4. Schema of the different stages of chronic mercury poisoning in Iraq.

blindness, severe cerebellar symptoms (mostly wing-beating), Parkinson symptoms, marked pyramidal tract symptoms, pseudobulbar symptoms, marked symptoms of a posterior column lesion and severe polyneuropathy with massive muscle atrophy.

In the fourth group the neurological picture reveals the apallic syndrome with coma vigile, sleep-wakefulness disturbance, absence of emotional reactions, divergence position of the eyes, marked increased oculocephalic reflex, increased jaw tonus and reflex, flex-stretch position of the limbs with increased tonus and tendency to hyperreflexia interfering more or less with polyneuropathy and Babinski phenomenon. In addition, massive motor primitive patterns and marked signs of a polyneuropathy are observed.

According to the clinical picture, the above described five cases have to be classified in the fourth group. In two out of the five patients the apallic syndrome was not fully developed at first. In the 15-year-old boy (case No. 2) the first examination showed symptoms of a prephase of the full stage with symptoms of a Klüver-Bucy syndrome as masturbation activity and object-mouth approach. His 17-year-old brother (case No. 3) was in the direct prephase state to full stage, with optic fixation as well as primitive emotional reactions. Four patients died in the full stage. In all cases laboratory findings gave objective evidence of mercury intoxication.

The principal treatment of patients with chronic mercury poisoning is dimercaprol (BAL), given in doses of 5 mg/kg body weight at 4-hour intervals during the first 2 days and the same dose during the next 10 days at 12-hour intervals. In addition to the BAL therapy high doses of the vitamin B group are also given. Administration of hypercaloric nutrition through nasal tube and cava catheter (3,000 calories daily) have to be performed. Generally speaking, important for the mercury intoxication is isolation and immediate hospitalization treatment with the above-mentioned therapeutic measures.

Early detection of cases and early treatment is likely to result in high recovery. In moderately severe and severe cases the residual com-

plaints usually are the peripheral nerve and posterior tract lesion symptomatology, as well as organic dementia, in some cases associated with cerebellar and Parkinson symptoms. The apallic stage usually is a grave condition.

According to *Kretschmer* (1940) the apallic syndrome from the pathophysiological point of view is a state of blockage of all higher cerebral functions with appearance of the autonomic functions of the brain stem. These disturbances are principally due to functional and not morphological lesions, therefore a remission is possible. The lesion can be in the cortex, white matter, thalamic region and the midbrain (*Gerstenbrand,* 1967). The remission depends upon the severity of the parenchymal damage. On the way to recovery the patient passes through typical stages like the stage of optic fixation and primitive emotions, the Klüver-Bucy stage, the Korsakow stage, etc. (*Gerstenbrand,* 1967). In 3 of our cases the full stage of an apallic syndrome was recognized, in the other two cases in the first examination a prephase could be observed, later passing into a full stage.

A lesion of one or several peripheral nerves of traumatic apallic patients can be found in 25 %. In apallic patients of other origin the percentage of peripheral lesion is higher, mostly the peroneus and ulnaris nerve are involved. As a reason for this a metabolic disturbance depending on the artificial nutrition combined with local pressure is discussed, in addition to toxic factors (*Gerstenbrand and Hamdi,* 1974). In cases with mercury poisoning the peripheral nerve lesion can be explained as a direct exogenous intoxication.

The pathological changes in Minamata disease of the Japanese cases described by *Takeuchi* shows the picture of a toxic encephalopathy characterized in the acute stage by an intense cerebral edema and damage to the capillaries causing the tissue to be distended and spongy. In the acute stage the ventricles are usually small due to the compression by the cerebral edema. In later stages a brain atrophy leads to a hydrocephalus. The capillaries are necrotic, degenerative changes are found in the nerve cells and myelin sheaths and there is proliferation of the glial cells.

In the spinal cord no marked changes in the acute stage except hemorrhages, edema and degeneration of neurons without loss of pyramidal cells in the anterior horn of the spinal cord are seen. In the chronic stage symmetrical demyelinization of the pyramidal tracts are found. In the acute stage no changes in peripheral nerves are seen but in the chronic stage granular degeneration of the myelin and localized demyelinization, macrophages containing pigmentary granules with lipids appearing and localized among the fibrous elements of the peripheral nerves are prominent.

References

Bidstrup, P.L.: Toxicity of mercury and its compounds (Elsevier, London 1967).

Gerstenbrand, F.: Das traumatische apallische Syndrom (Springer, Wien 1967).

Gerstenbrand, F. und Hamdi, T.: Zur Klinik der organischen Quecksilber-Vergiftung. Int. Danube-Symp. Neurol., Neuropathol. Paediat. Neurol., Poznan 1974.

Gerstenbrand, F. und Lücking, C.H.: Die akuten traumatischen Hirnstamm-Syndrome. Arch. Psychiat. NervKrankh. *213:* 264–281 (1970).

Hunter, D. und Russell, E.S.: Focal cerebral and cerebellar atrophy in a human subject due to organic mercury compounds. J. Neurol. Neurosurg. Psychiat. *17:* 235–242 (1954).

Kitamura, S., et al. (1960): cited after Takeuchi (1958).

Kretschmer, E.: Das apallische Syndrom. Z. ges. Neurol. Psychiat. *169:* 576–579 (1940).

Kurland, L.T.; Faro, S.N., and Siedler, H.: Minamata disease. The outbreak of neurologic disorder in

Minamata, Japan, and its relationship to the ingestion of seafood contaminated by mercury compounds. Wld Neurol. *1:* 370–395 (1960).

Matsumoto, H.; Koya, G., and Takeuchi, T.: Fetal Minamata disease. A neuropathological study of two cases of intrauterine intoxication by a methyl mercury compound. J. Neuropath. exp. Neurol. *24:* 563–570 (1965).

McAlpine, D. and Araki, S.: Minamata disease; an unusual neurological disorder caused by contaminated fish. Lancet *ii:* 629–632 (1958).

Pentschew, A.: Quecksilbervergiftung; in Handbuch der speziellen pathologischen Anatomie und Histologie, vol. XIII/2B, p. 2007 (1958).

Takeuchi, T.: Pathological studies on Minamata disease. In Japanese. Annual Report of Cooperative Research (Medicine). Ministry Education, No. 12, UDC 61 (87), p. 239 (1958).

Takeuchi, T.: Pathology of Minamata disease. Minamata disease (organic mercury poisoning) (Shuhan, Tokyo 1968).

Takeuchi, T. and Morikawa, N.: Pathological studies on Minamata disease, especially on the cause of this disease. In Japanese. Psychiat. Neurol. Jap. *62:* 1850–1861 (1960).

Takeuchi, T.; Morikawa, N., Matsumoto, H., and Shiraishi, Y.: A pathological study of Minamata disease in Japan. Neuropathology *2:* 40–51 (1961).

Tokuomi, H.; Okajima, T.; Kanai, J.; Tsunoda, M.; Ichiyasu, Y.; Misumi, H.; Shimomura, K., and Takaba, M.: Minimata disease. Wld Neurol. *2:* 536–545 (1961).

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