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Minamata Disease—Review

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Abstract

Minamata disease is the name given to a neurological syndrome caused by organic mercury intoxication. Most commonly it results from consumption of methylmercury contaminated seafood and in severe cases is classically manifested by concentric constriction of the visual fields, ataxia and sensory disturbance in the distal extremities. The radiographic and neuropathological findings parallel the clinical picture and typically consist of lesions selectively involving the visual cortex, cerebellum and postecentral gyri.

Keywords

Minamata Disease, Methylmercury Poisoning

1. Introduction

Mercury is encountered in both inorganic-elemental or mercury salts, and organic-alkylated forms. Each form possesses different toxic properties and intoxication with each form yields a distinct clinical and neuropathological picture.

Neuro-toxic effects of inorganic mercury have been known for at least two centuries. Some of the classical manifestations of inorganic mercury poisoning are exemplified by the 19th century Mad Hatters—workers in the felting industry chronically exposed to elemental mercury vapors. These include confused speech, distorted vision, constellation of irritability, excitability, tendency to weep, anxiety, insomnia, and social withdrawal—known as erethism, fine tremors of the hands and feet (so-called Danbury Shakes, from hat makers in Danbury, Connecticut), personality changes, memory loss, inability to concentrate and occasional hallucinations [1].

However, the devastating effects of the organic mercury exposure, in particular methylmercury, were acknowledged only in the second half of the 20th century. Whereas industrial and accidental exposure to inorganic mercury has become rare, a more insidious and devastating methylmercury poisoning from in-

gestion of contaminated food, has emerged as a serious potential health hazard.

2. Historical Perspective

Although the first report of human methylmercury poisoning has been published as early as in 1940 by Hunter *et al.* [2], the condition has become generally recognized only in the 1960s when causal relationship could be established between consumption of contaminated seafood and mysterious disease causing neurological symptoms and death among several thousand inhabitants of the Minamata Bay in Kumamoto prefecture of the southwestern isle of Kyushu in Japan [3].

The disease presented with sudden onset. The patients complained of a loss of sensation and numbness in their hands and feet, inability to grasp small objects, unsteady gait and voice change. Many complained of difficulties seeing, hearing and swallowing. In general these symptoms deteriorated and were followed by convulsions, coma and eventually death. Not only humans were affected—Minamata Bay's cats had been seen to have convulsions, go mad and die. Locals called it the "cat dancing disease", owing to their erratic movement [3].

After years of investigations the cause of the epidemic was identified as methylmercury from the wastewater dumped into the bay from 1932 to 1968 by the nearby chemical plant belonging to the Chisso Corporation [4]. The methylmercury had bio-accumulated in the local fish and shellfish which were consumed by local fishermen and their families. The condition has become known as Minamata disease (or Chisso-Minamata disease).

1965, another epidemic of Minamata disease was reported in the Agano River basin in Niigata Prefecture. It was also due to consumption of contaminated fish [5].

The Minamata disease patients officially recognized at Minamata and Niigata amount to a population of 2263 and 690 respectively [6]. In addition, those who are suspected of suffering from Minamata disease in Japan (with chronic and mild symptoms) amount to a population of about 12,000 [4].

The largest outbreak of methylmercury poisoning happened in the winter of 1971-1972 in rural Iraq, where farmers and their families ingested homemade bread made from seed wheat treated with a methylmercury fungicide. There were 6530 reported cases of poisoning [7].

Since then only sporadic isolated cases of human organic mercury poisoning could be found in the English-language medical literature. Notably, we found a case of three British industrial workers exposed to mercury acetate [8] and a case of an American family who consumed pork contaminated with methylmercury [9]. There have been reports of possible poisoning from China, Canada, and the Amazon [10] [11] [12]. However, neither of these reports contained neuropathological or radiographic data.

3. Clinical Findings

Diagnostic guidelines for Minamata disease include sensory disturbance in the

distal extremities, ataxia, loss of balance, concentric constriction of the visual fields, impairment of gait, speech and hearing, muscle weakness, tremor and nystagmus [6]. Mental disorder and disturbances of taste and smell are also present occasionally. Sensory disturbance and constriction of the visual field were observed among 100% of Minamata disease patients, impaired coordination among 93.5%, dysarthria among 88.2%, hearing impairment among 85.3%, gait abnormalities in 82.4% and tremor among 75.8% [13].

In 1962, it was established that methylmercury causes fetal poisoning in the exposed mother by crossing the placenta. It was called congenital Minamata disease. At least 64 cases of it have been reported to date. Its symptoms include 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 and pyramidal signs [14].

4. Neuropathological Findings

In acute cases of Minamata disease, the brain is swollen and the leptomeninges edematous and turbid [15]. Focal lesions seen in the Minamata disease cases have characteristic anatomical distribution. The brains of patients who presented with acute onset of symptoms and died within two months showed loss of neurons with reactive proliferation of glial cells, micro-cavitations, vascular congestion, petechial hemorrhage, and edema in the cerebellum and cerebral cortex, predominantly in the calcarine region, precentral, postcentral and transverse temporal gyri [15]. The most conspicuous destructive lesions were found in the anterior portions of the calcarine cortex, particularly along the calcarine fissure. Postcentral, precentral, and temporal transverse gyri were affected to a lesser degree. Lesions in the precentral cortex invariably resulted in the development of secondary bilateral degeneration of the pyramidal tracts [15].

In the cerebellum, the lesions occurred deeper in the hemispheres with relative sparing of the cerebellar cortex [15]. The granular cell population was classically most affected, compared to Purkinje cells—the so-called granular type of cerebellar atrophy.

The neuropathological changes in the patients with acute onset of symptoms who survived for long periods of time demonstrated neuronal loss with reactive proliferation of glial cells in the same anatomic distribution [15].

Methylmercury-exposed common marmosets develop anatomical lesions very similar to those of humans with Minamata disease. The lesions in the exposed animals consisted of neuronal loss with reactive gliosis in the calcarine cortex and in the cerebellum [16].

Studies of methylmercury effects in common marmosets also showed damage to peripheral nerves, which at least in part contributes to the sensory symptoms observed in Minamata disease patients [17]. This finding is further corroborated by autopsy studies of Minamata disease patients [18]. In the peripheral nerves, sensory nerves were more affected than motor nerves [18].

Pathological changes in the cerebrum in fetal Minamata disease were different from those found in children and adult cases. The changes in fetal brains were less localized to a specific site and showed hypoplasia or developmental arrest, rather than destruction of neurons [19] [20].

Usuki *et al.* have studied the effects of methylmercury ingestion on skeletal muscles in rats and has conclusively demonstrated that methylmercury disturbs mitochondrial energy metabolism in skeletal muscle, which can also in part explain the symptoms of extremity weakness and wasting, and muscle cramps, often seen in Minamata disease [21].

The exact mechanism by which methylmercury intoxication leads to biological damage is not fully understood.

The high thiol reactivity of methylmercury, as well as all mercury compounds, has been suggested to be the basis of their harmful biological effects. However, there is a clear selectivity of methylmercury for specific cell types and brain structures, which is not yet fully understood. The main mechanisms proposed so far are inhibition of protein synthesis, microtubule disruption, increase of intracellular calcium with disturbance of neurotransmitter function, oxidative stress and triggering of excitotoxicity mechanisms[22] [23] [24].

A plausible hypothesis as to the mechanism for the selective vulnerability of certain brain regions in Minamata disease postulates that the observed lesions are the result of ischemia secondary to compression of deep sulcal arteries from methylmercury-induced cerebral edema [16]. It is hypothesized that white matter edema occurring during acute methylmercury poisoning leads to compression of deep sulcal arteries and focal vascular insufficiency of the cerebellar, calcarine and somatosensory regions. This hypothesis has been at least partially corroborated by data from the experiments with common marmosets whose brain has two distinct deep sulci, the calcarine and Sylvian fissures. Brains of methylmercury exposed animals showed high contents of methylmercury and edema of the cerebral white matter acutely, and cortical atrophy along deep sulci, similar to human Minamata disease cases, later on [16]. Additionally, significantly reduced regional cerebellar blood flow was demonstrated in Minamata patients, even those without cerebellar atrophy, compared to normal controls, giving further support to the vascular hypothesis of selective brain damage in methylmercury poisoning [25].

5. MRI Findings

The typical radiographic findings in Minamata disease reflect its typical neuropathological lesions. MRI of the brains of Minamata disease patients classically demonstrate significant atrophy of the visual cortex, the cerebellar vermis and hemispheres, and the postcentral cortex consistent with the three characteristic manifestations of this disease: the constriction of the visual fields, ataxia, and sensory disturbance. The visual cortex is typically slightly hypo-intense on T1-weighted images and hyper-intense on T2-weighted images, probably representing the pathologic changes of status spongiosus [9] [25] [26] [27] [28].

Valk and van der Knapp described a case of intoxication with mercury-containing fungicide, in which T2 gradient-echo MRI showed low signal intensities in the cerebellum and occipital lobes [29]. These were thought to be due to local inhomogeneity of the magnetic field caused by the mercury itself.

Conversely, cases of inorganic mercury poisoning both acute and chronic demonstrate no specific neuropathological findings [15]. Brain MRI of the affected patients could be normal, demonstrate diffuse cerebral and cerebellar atrophy or multiple reversible T2 hyperintense lesions in cerebral white matter, globus pallidus, and putamen [1] [30] [31].

6. Treatment

Other than supportive therapy, decontamination and removal from the source of exposure, there are no clear guidelines as to treatment of methylmercury poisoning. In cases of acute ingestion of organic mercury contaminated products, gastric lavage and GI decontamination with activated charcoal can be of benefit. Although chelation therapy with 2,3-dimercaptosuccinic acid (DMSA) plays a role in treatment of inorganic mercury exposure, it is of limited benefit in cases of methylmercury poisoning. Furthermore, the neurological sequelae of Minamata disease are irreversible.

7. Conclusion

Severe methylmercury intoxication results in characteristic irreversible neuropathological abnormalities which manifest clinically most frequently as constriction of the visual fields, ataxia and sensory disturbance. Radiographically they present classically as selective atrophy of the cerebellum, calcarine and postcentral gyri. The degree of neuropathological alterations is likely to be proportional to the amount of mercury and to the acuteness of exposure. It seems that lower levels of absorbed methylmercury result in milder forms of the disease, which do not satisfy the clinical criteria of Minamata disease and do not necessarily lead to the classical radiographic findings.

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