Chronic Neurological Disease Due to Methylmercury Poisoning

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ABSTRACT: Organic mercury, especially methylmercury, poisoning causes chronic neurological disease predominantly affecting the brain. There have been documented exposures from eating fish from contaminated waters in Japan and in northwestern Ontario and in Iraq from eating bread made from seed wheat treated with methylmercuric fungicide. The neurological disease is called Minamata disease in Japan. Visual field constriction due to involvement of the calcarine cortex, sensory disturbance due to involvement of the somatosensory cortex, and cerebellar ataxia due to involvement of granule cell neurons of the cerebellum are common and characteristic features due to methylmercury poisoning. Other neurological features include dysarthria, postural and action tremor, cognitive impairment, and hearing loss and dysequilibrium. In contrast, peripheral nerve disease is more characteristic of inorganic mercury intoxication. Similarly, psychosis is more typical of exposure to inorganic mercury, which has been documented in the felt hat industry ("mad hatter"). Laboratory tests (e.g., on blood and hair and toenail samples) are of limited value in the assessment of chronic neurological disease due to mercury poisoning because they may not reflect remote neuronal injury due to mercury. Methylmercury also causes injury to fetal brains during development. There is no effective treatment.

RÉSUMÉ: Des maladies neurologiques chroniques attribuables à un empoisonnement au méthylmercure. L'empoisonnement au mercure organique, en particulier le méthylmercure, est la cause de maladies neurologiques chroniques qui affectent surtout le cerveau. Des cas d'exposition au méthylmercure ont ainsi été répertoriés au Japon et dans le nord-ouest de l'Ontario après que des individus ont consommé des poissons pêchés dans des eaux contaminées. En Iraq, c'est plutôt la consommation de pain confectionné à partir de semences de blé traitées avec un fongicide à base de méthylmercure qui a été pointée du doigt. Au Japon, la maladie neurologique qui en résulte a été baptisée *Minamata*. Parmi les caractéristiques habituelles de l'empoisonnement au méthylmercure, on peut citer: 1) la constriction du champ visuel en raison de l'impact de la scissure calcarine du lobe occipital; 2) des perturbations sensorielles attribuables au rôle du cortex somatosensoriel; 3) et l'ataxie cérébelleuse causée par l'action des cellules granulaires du cervelet. D'autres caractéristiques d'ordre neurologique incluent notamment la dysarthrie, des tremblements de la posture ou au moment d'exécuter une action, une déficience cognitive, une perte auditive et des symptômes de déséquilibre. En revanche, il faut rappeler que les maladies des nerfs périphériques sont davantage caractéristiques d'une intoxication au mercure inorganique. De même, les cas de psychose demeurent davantage typiques d'une exposition à ce type de mercure, ce qui a été documenté dans l'industrie des chapeaux en feutre (on parlait jadis de la « maladie des chapeliers fous »). Des tests effectués en laboratoire, par exemple à partir d'échantillons sanguins, capillaires ou d'ongles d'orteils, ont une valeur limitée quand il s'agit d'évaluer une maladie neurologique chronique attribuable à un empoisonnement au mercure. En effet, de tels test pourraient très bien ne pas rendre compte des lésions neuronales isolées causées par cet élément chimique. Mentionnons aussi que le méthylmercure entraîne des lésions cérébrales pendant le développement du fœtus. À cet égard, il n'existe aucun traitement efficace contre cette affection.

Mercury is ubiquitous in the environment and its presence is often not associated with human disease. There are elemental, inorganic, and organic forms of mercury. This review will focus on the effects of organic mercury, especially methylmercury, on the human nervous system. In Japan inorganic mercuric sulfate, which has been used as an industrial catalyst for acetaldehyde synthesis, was discharged into the sea by an industrial plant near the Japanese fishing village of Minamata in the 1950s[1] and later also into the Agano River in Niigata, Japan in the 1960s.[2] Inorganic mercury is converted into methylmercury (CH_3Hg+) in industrial plants or by microorganisms in aquatic sediments and then mercury enters the aquatic food chain and is present in muscle tissues of predatory fish and may be consumed by humans in fish fillets. In many patients the exposure to mercury occurs over long periods, typically years, and this food-borne poisoning that causes neurological disease is called Minamata disease in Japan and thousands of cases have been documented. Consumption of bread made from seed wheat treated with methylmercuric fungicide in Iraq in 1971 and 1972 caused thousands of cases of

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severe intoxication and many deaths,[3] There were earlier similar epidemics in Iraq in 1956 and 1960.[4]

In 1970 it was recognized that the English—Wabigoon River system in northwestern Ontario, Canada was contaminated with mercury. It was later determined that the point source of the contamination was a chlor-alkali plant, Dryden Chemicals Limited. The plant had dumped untreated mercury wastewater into the Wabigoon River between 1962 and 1970, which contaminated the rivers and lakes downstream and affected the Grassy Narrows First Nation and Wabaseemoong Independent Nations (formerly Islington Band, formally Whitedog).[5] Harada et al[6] reported neurological disease meeting criteria for methylmercury poisoning affecting residents of Grassy Narrows, Ontario. In 1985 an out of court settlement was negotiated by Wabaseemoong Independent Nations and Grassy Narrows First Nation with the Canadian government, the province of Ontario, and two paper companies for all claims due to mercury contamination in the English—Wabigoon River system and legislation was subsequently enacted to carry out the terms of the settlement. Members of these communities whose health may have been affected by mercury poisoning are potentially eligible for an award from an established disability fund upon application and a medical evaluation.[5]

NEUROLOGICAL DISEASE CAUSED BY METHYLMERCURY

It has been recognized that methylmercury causes selective injury of the nervous system of humans with only relatively minor involvement of other organs, including gastrointestinal tract inflammation, fatty degeneration of the liver and kidneys, alteration of pancreatic islet cells, hypoplasia of bone marrow, and atrophy of lymph nodes.[7] The brain is the primary target of organic mercury exposures, whereas peripheral nervous system involvement is more common with elemental and inorganic mercury exposures. Neuropathological studies have been helpful in determining the neuroanatomical sites of neuronal injury, and there have been autopsy reports on hundreds of cases of Minamata disease in Japan. MRI has also demonstrated lesions involving the cerebral cortex and cerebellum.[8] There is symmetrical involvement of lesions in the brain.[9] With acute exposure in Iraq, symptoms began insidiously 2-6 weeks after ingestion of the contaminated bread.[10] There may be a long latency period lasting weeks to months from the time of exposure until the onset of symptoms, although the explanation for the long latency period remains unclear.[11] There is evidence that there may be delayed neurotoxicity of methylmercury with aging that may be manifested many years after cessation of exposure.[12] The fetal brain is more susceptible than the adult brain to the toxic effects of methylmercury and may be affected as the result of maternal exposure.[13] The migration and division of neurons is inhibited, resulting in disruption of the cytoarchitecture of the developing brain[13] and severe mental and motor developmental deficits.

PATHOLOGY AND PATHOGENESIS

Pathological studies have been reported in Minamata disease.[9,14,15] The most severe damage is noted in the cerebral and cerebellar cortices with neuronal loss. Many autophagosomes are present, particularly in cerebral neurons.[14] Mercury granules may be detected.[14] Major mechanisms of methylmercury-induced cell damage include disruption of calcium homeostasis, induction of oxidative stress, and interactions with sulfhydryl groups.[16] Targeting of proteins and peptides containing cysteine and methionine contributes to the cytotoxicity of methylmercury.[16]

BRAIN DISEASE

Unlike inorganic mercury intoxication, the symptoms of organic mercury poisoning chiefly involve the brain.[17] Typical signs of methylmercury poisoning include cerebellar ataxia, dysarthria, and constriction of the visual fields, which is known as the Hunter-Russell triad after their publication from London, United Kingdom in 1954.[9] These three clinical features are often accompanied by hearing impairment and sensory disturbance. In the brain the injury is most severe involving the cerebral cortex and the cerebellar cortex, whereas the brainstem is less affected and the spinal cord is least involved.[14] In Minamata disease in Japan, there was prominent degeneration and atrophy of the cerebellum due to toxicity to granule cell neurons and of the calcarine cortex.[9] Experimental studies in common marmosets confirmed the selective vulnerability of the cerebral cortex in methylmercury poisoning.[18]

Visual Field Constriction

Impairment of visual acuity associated with bilateral concentric constriction of the visual fields is caused by damage to the primary visual cortex in the calcarine region, and is regarded by many authorities as the most pathognomonic finding in Minamata disease. Pathologically, atrophy is most marked at the anterior ends of the calcarine fissures with relative sparing near the occipital poles, which explains the preservation of central vision that is located at the posterior extremity of the visual cortex.[19] There is loss of neurons in the calcarine area and the histopathological appearance progresses to status spongiosis.[15] A study of eight patients with Minamata disease showed moderate to severe constriction of the visual fields with central vision ranging from 7° to 42° from the point of fixation. MRI showed dilation of the ventral portion of the calcarine fissures and T2-weighted images showed hyperintense lesions sparing the most posterior portion of the striate cortex.[20] In a slightly smaller series of seven patients with concentric constriction of the visual fields reported by the same group 3 years earlier, it was noted that all of the patients also had sensory disturbance and ataxia, indicating that the characteristic visual field impairment was not an isolated finding.[8] The prevalence of constriction of visual fields was estimated to be about 29% among residents of Minamata.[21]

Ataxia and Dysarthria

Cerebellar ataxia is present in 81%-94% of patients with Minamata disease and in 95% of patients in Iraq with methylmercury poisoning.[4] There is often associated dysarthria with cerebellar features (scanning speech), which occurred in 72% (33 of 46) of patients with methylmercury poisoning after eating bread from treated wheat in Iraq.[4] Nystagmus is not usually observed. Pathologically there is atrophy of the cerebellum with a profound loss of cells in the granular cell layer with relative sparing of Purkinje cells; changes are most marked in the depths of the sulci with relatively normal cortex at the surface.[19] There is marked loss of granule cell neurons and also

of Golgi cells. Other movement disorders, including choreiform or athetotic movements and hemiballismus, are observed in only a minority of patients.[22]

Hearing Loss and Disequilbrium

Many patients experience hearing loss. Hearing loss is due to injury in the primary auditory area in the region of the transverse gyrus in the temporal lobes, but may also be due to cochlear involvement. The prevalence of hearing difficulties was estimated to about 29% among residents of Minamata[21] and in 19% of 53 patients with methylmercury poisoning in Iraq.[4] Over time some patients show improvement of hearing impairment, whereas others have deterioration that may be, at least in part, related to aging.[23] In contrast, there was little significant change over time in caloric nystagmus test and body equilibrium tests.[23] Dizziness and unsteadiness were observed in 98 cases out of 144 (68%) with organomercury intoxication in Niigata, Japan.[24]

Tremor

With methylmercury poisoning in Iraq, 7 of 53 (13%) patients had intention tremor and flapping and static tremor was observed in one (2%) each.[4] Postural and action tremor are recognized in Minamata disease. Yamanaga[25] evaluated eight patients with Minamata disease who were unselected with respect to tremor. He found that seven of the eight (88%) patients with Minamata disease had postural and action tremor. The mean frequency of the postural tremor was 7.1 Hz for Minamata disease versus 8.7 Hz for essential tremor and 9.5 Hz in normal subjects (the frequency declined with age), whereas the mean amplitude was 1.8 mV for Minamata disease versus 1.1 mV in normals. Interestingly, one of the eight patients had a much lower postural frequency of 4.5 Hz. Yamanaga[25] speculated that the tremor in Minamata disease may be related to the involvement of cerebellar granule cell neurons affecting cerebellar output.

Cognitive Impairment and Psychiatric Features

Mental confusion is commonly observed in seriously ill patients with Minamata disease and patients may be drowsy or restless.[22] Progression may occur to stupor or coma in fatal cases.[22] Three of 27 patients (11%) with methylmercury poisioning in Iraq had dementia.[4] Psychiatric features include depression and irritability, which were observed in 74% and 44% of 43 patients, respectively, with methylmercury poisoning in Iraq.[10] In comparison, more severe psychiatric symptoms with psychotic features have been observed with exposure to inorganic mercury such as the "mad hatter" in the felt hat industry.[10]

Somatosensory Disorder and Peripheral Nerve Disease

Numbness and paresthesias with associated sensory impairment in the distal extremities occurs in the majority of patients with Minamata disease. In Japan paresthesias of the extremities was used as the gold standard for identification of Minamata disease due to methylmercury poisioning because paresthesias usually appear earliest and have the lowest threshold in outbreaks in Japan and also in Iraq.[3] Mild cases may manifest as paresthesias only.[26] In comparison, the prevalence of paresthesias in non-exposed regions of Japan was less than 1.1%.[26] In Japan a diagnosis of Minamata disease using diagnostic criteria established in 1977 required paresthesias plus cerebellar ataxia, disturbed sense of equilibrium, concentric constriction of the visual fields, or CNS ophthalmologic or otologic disturbance. However, more recent work indicates a sensitivity of the criteria of only 66%, hence, the requirement for paresthesias results in an underestimation of Minimata disease.[26] In most cases deep tendon reflexes are preserved or hyperactive rather than reduced or absent.[21,27] An associated perioral sensory disturbance is common, with an "onion peel" somatosensory distribution indicating involvement of the cerebral cortex rather than due to a localization involving peripheral nerves. Electrophysiological testing and somatosensory evoked potentials clarified that the lesion associated with the persistent sensory disorder is in the somatosensory cortex (in the postcentral gyrus) and not in peripheral nerves.[28] The findings of evenly distributed increased touch thresholds in both distal and proximal locations and increased two-point discrimination thresholds in both forefingers and lips also confirmed localization in the somatosensory cortex.[27] Early reports indicated that peripheral nerves were histopathologically intact.[19] Electrophysiologic and histopathologic studies on sural nerves of Minamata disease patients showed no differences with control subjects.[29] Takeuchi[7] described pathological findings in 17 cases of Minamata disease and found no changes in either the peripheral nerves or spinal cord. However, in a report of six patients with sural nerve biopsies[30] and one patient with an autopsy,[31] all with typical Minamata disease with clinical evidence of brain involvement, there was pathological evidence of peripheral nerve degeneration. The biopsies showed irregularly shaped myelin sheaths, incomplete regeneration of nerve fibers, and collagen increase.[30] The autopsy case showed Wallerian degeneration of the fasciculus gracilis and endoneurrial fibrosis and loss of nerve fibers and the presence of Bünger's bands in dorsal roots and in sural nerve.[31] Hence, it is not clear to what extent sensory symptoms in patients with Minamata disease reflect involvement of somatosensory cortex versus peripheral nerves, but no cases have been reported exclusively with peripheral nerve degeneration.

LABORATORY INVESTIGATIONS

When a meal containing methylmercury is eaten, peak mercury levels occur 4-14 hours later and then several hours more for distribution in the body; it subsequently takes months for elimination.[32,33] A variety of laboratory investigations can be performed to detect the presence of mercury in the body, including blood mercury levels[34] and assays on scalp hair samples[32] and toenails.[35] Toenails are considered biomarkers for mercury exposure occurring 3-12 months before exposure[35] and possibly longer. However, these assays are of limited value because mercury is excreted slowly from the body and assays may not reflect the situation when previous neuronal injury occurred many years earlier resulting in chronic neurological disease. This highlights the need for detailed clinical assessments in assessing neurological deficits related to mercury poisoning.

TREATMENT

Unfortunately, there is no known therapy that is effective for reducing neuronal damage. Methylmercury exposure from dietary sources (e.g., fish) usually occurs over a long period lasting months to years. By the time that neurological symptoms and

signs develop, irreversible neuronal damage has already occurred and therapy with chelators is not effective.[13] Of course, it is important to eliminate a contaminated dietary source in order to prevent further exposure and damage.

CONCLUSIONS

Methylmercury poisoning causes chronic neurological disease predominantly due to direct neuronal injury in the brain, particularly involving the cerebral cortex and granule cells in the cerebellum. Detailed clinical assessments are needed to evaluate the extent of neurological deficits due to mercury poisoning because laboratory investigations are of limited value and do not assess past neuronal injury that may be due to high-dose exposure that occurred decades earlier.

DISCLOSURE

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