Trace Elements and Nervous and Mental Diseases

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Abstract: Relationships between Al, Fe, and Mn and Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and parkinsonism are outlined. These diseases are thought to be multifactorial, and trace element abnormalities are suspected of being risk factors. Al and Fe are suspected of being involved in the formation of neurofibrillary tangles (NFT) and senile plaque in AD. The Kii Peninsula of Japan has been the focus of ALS, and an association between environmental factors and its occurrence is suspected. Environmental metal analyses in this area has revealed low contents of Ca and Mg and high contents of Al and Mn in the drinking water and soil. Al deposition has been observed in the brain tissue of patients from Kii Peninsula. Cell loss has been noted in the spinal cord and cerebrum of animals chronically given a low Ca/Mg high-Al diet, and an etiological association with these trace elements was suspected in ALS cases from this area. Mn is known to induce the development of extrapyramidal manifestations. Although the clinical manifestations of Mn-exposure parkinsonism and Parkinson's disease are different, involvement of environmental factors has been speculated in the onset of Parkinson's disease, and there is concern about air pollution by Mn. In addition, there are cases of Al encephalopathy in which an association with high-calorie infusion therapy and Al-containing medical materials is suspected.

Key words: Aluminum; Neurotoxicity; Amyotrophic lateral sclerosis foci; Amyotrophic lateral sclerosis; Iron; Manganese

Introduction

A variety of trace elements have been shown to be involved in nervous and mental diseases. In this article, the etiological associations will be described between iron (Fe), zinc (Zn), and aluminum (Al) and dementia, especially Alzheimer’s disease; calcium (Ca)/magnesium (Mg) deficiencies and excessive trace elements, such as aluminum and manganese (Mn), in amyotrophic lateral sclerosis (ALS), parkinsonism induced by manganese poisoning; dialysis encephalopathy and aluminum; and aluminum poisoning by medical materials.

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Alzheimer’s Disease and Trace Elements

In 1965 Klazo et al.\(^1\) reported the development of abnormal intracellular accumulations of neurofilaments (NFs) when they administered aluminum phosphate into the brain of experimental animals. Since the changes closely resembled the neurofibrillary tangles (NFTs) of Alzheimer’s disease, attention was focused on an etiologic association. Epidemiologic surveys in the United Kingdom, the United States, Canada, and Norway have shown high prevalences of Alzheimer’s disease in regions where the aluminum concentration in tap water is high. Metal analyses have also shown higher aluminum concentrations in the brains of Alzheimer’s disease patients than in controls, and aluminum deposition has been demonstrated in NFTs and senile plaques.

In contrast, many reports about the association between aluminum and Alzheimer’s disease have been negative. Since aluminum displays an aggregating action \textit{in vitro}, at least on cytoskeletal proteins such as NF, the possibility that it plays some sort of etiologic role cannot be ruled out, and further investigation appears to be needed.

Aluminum binds to the phosphate groups of DNA and cytoskeletal proteins \textit{in vitro} and induces aggregation of amyloid protein and excessive phosphorylation of tau protein. It causes irreversible changes in the structure of these proteins, and hyperphosphorylated fibers are thought to cause cell death by accumulating and impairing axonal transport. The cytotoxic mechanism of aluminum is also suspected of being caused by the production of free radicals, such as hydroxyl radicals, as a result of a transition from $\text{Al}^{2+}$ to $\text{Al}^{3+}$.

Next, there is the neural cytotoxicity widely known to be caused by iron. The globus pallidus, red nucleus, substantia nigra, cerebellar dentate nucleus, and cerebral motor area contain large amounts of non-heme iron. The values are low in newborn infants, but rapidly increase until the late teens. They remain almost the same in the 30s to 50s, before slowly rising in the brain again in old age. The iron is specifically distributed in the oligodendrocytes in the central nervous system and in the Schwann cells in the peripheral nervous system, and it binds to ferritin. By storing iron in its molecules, ferritin plays a role in the intracellular utilization and inactivation of iron. As an essential element in tyrosine hydroxylase, the action of iron is important in the synthesis of dopamine, norepinephrine, serotonin, and GABA.

In contrast, iron ions cause peroxide-radical damage by changing from an oxidized to a reduced form. They also reversibly hyperphosphorylate and insolubilize tau protein and contribute to the formation of NFT.\(^2\) It has been reported that there is increased iron content in the brain tissue of Alzheimer’s disease patients as well as increased ferritin in senile plaques and microglia, increased iron and zinc content, and decreased selenium (Se) content (selenium is speculated to have a preventive effect against the cytotoxicity produced by toxic elements).\(^3\)

In addition, there is increased Fe-binding protein P97 and melatonin in the serum, spinal fluid, and brain tissue of Alzheimer’s patients; and glutathione transferase, which possesses lipid-peroxide-degrading activity, is decreased and there are changes in metallothionein. Cytotoxicity caused by metal elements, such as iron and aluminum, is suspected, and use of p97, etc., has been assessed as a serum biomarker for Alzheimer’s disease.\(^4\) It is hard to imagine that these abnormal findings of chemical elements are the sole cause of Alzheimer’s disease, but they appear to be associated as risk factors.

Superficial siderosis is known as another central nervous system disorder caused by iron, and chronic, repeated bleeding in notably chronic subarachnoid hemorrhages, dural lesions, cervical spinal root lesions, vascular tumors, and vascular malformations, results in deposition of iron in the dura mater and
the surface of the central nervous system. After an asymptomatic interval of 4 months to 30 years, it leads to sensory deafness (95%), cerebellar ataxia (88%), pyramidal disorders (76%), dementia (24%), and urination disorders (24%).

**Amyotrophic Lateral Sclerosis (ALS) and Calcium, Magnesium, and Aluminum**

ALS is a degenerative disease that systematically affects upper and lower motor neurons and is characterized by severe neuronal loss of Betz cells in the motor cortex, and motor neurons in the brain stem, and spinal anterior horn cells with degeneration of the pyramidal tracts. Its prevalence is almost the same in every region of the world, and it is said to be 0.8–6.4 per 100,000 people, with an annual incidence rate of 0.4–2.6. In the 1960s, the prevalence of ALS in the Kozagawa region and Hobara region of the Kii Peninsula and in the southern part of Guam Island reached levels of 10 to 100 times higher than in other regions. The incidence of new cases began to decline in the 1970s, and it dramatically decreased in the 1980s to only several times the level in other areas. A recent repeat survey showed that the regional differences in the Kii Peninsula as a whole have tended to disappear due to the movement of the population to other areas, but, the annual incidence of ALS in the southern part of the Kii Peninsula is still high.

The cause and pathogenetic mechanism of ALS are still unknown, but attention is being focused on the free-radical and excitatory-amino-acid cytotoxicity hypothesis, superoxide dismutase (Cu/Zn SOD) gene abnormalities, and ubiquitin-proteasome system damage. Involvement of environmental factors appears to be important in ALS foci, in addition to these factors.

Another area of focus for ALS lies above the Mariana volcano zone that runs geologically north to south through the Western Pacific. There is high annual rainfall, and the soil is strongly acidic in this region. The soil and the water used in daily living were characterized by low calcium and magnesium levels as well as high levels of toxic elements, including manganese and aluminum according to the survey findings obtained during the 1960s and the 1970s. In addition to the ordinary pathological findings in ALS, the autopsy brain and spinal cord tissue in Guam ALS/parkinsonism-dementia (PD) and Kii ALS is characterized by the presence of NFTs. Element analysis revealed deposition of calcium and aluminum at the sites of degeneration, and in the nuclei and nucleoli of degenerated neurons, Bunina bodies, and NFTs. In considering these combined findings, the neuronal degeneration of Kii ALS has been speculated to be due to these elements.5)

When aluminum was injected into the brains of experimental animals, extensive abnormal...
intracellular accumulation of NFs (neurofibrillary change; NFC) was observed in the cerebrum and spinal cord, and numerous spheroids began to appear in the anterior horns of the spinal cord in the early stages. This abnormal accumulation of NFs strongly resembled the spheroids/chromatolysis, which are characteristic pathological findings in the early stages of ALS. NFC differs from NFTs at the electron-microscopic level, but tau, ubiquitin, MAP-2, amyloid precursor protein, etc., have been observed immunohistochemically, and similarities between the two have been pointed out.

To explain the occurrence of NFTs in the ALS from the focused area, the author and colleagues investigated the cytotoxicity of aluminum due to metal ion interactions in the environment of the Kii area. More specifically, experimental animals were chronically administered a low-CA/Mg high-Al diet. Neuropathological examinations of these animals showed a decrease in the spinal cord anterior horn cells, and cerebral cortical neurons, an increase in spheroids, and an appearance of anti-PHF (abnormal phosphorylated tau)-antibody-positive neurons.

Aluminum is a toxic element, and only about 1% of the amount ingested is absorbed by the gastrointestinal tract. Approximately 80% of the aluminum in the blood binds competitively with iron to transferrin, and a portion of the remainder binds to low-molecular-mass molecules, such as citric acid, and is transported. Aluminum’s entry into the brain is mediated by transferrin receptors, and it is bound to glial transferrin. Aluminum absorption from the intestine is promoted under low-Ca/Mg conditions, and when aluminum is administered chronically, it is thought to accumulate in the brain and spinal cord and to have cytotoxic effects. Clinically, anemia, bone damage, and dialysis encephalopathy are known to develop in aluminum poisoning. As mentioned above, aluminum has been found to bind irreversibly to phosphate groups in vitro and to be widely neurotoxic, e.g., by inhibiting polymerization/depolymerization of tau and NF, inhibiting Ca-binding proteins, such as calmodulin, and Ca-dependent enzymes. A mechanism in which mild damage caused by microamounts of aluminum incorporated from the environment, food, etc., accumulates. It has been speculated that cell death occurs when it exceeds a certain level, and abnormalities in interactions between elements appear to be important in terms of assessing the pathogenesis of the ALS occurring in foci.

Parkinsonism and Manganese

The first mention of manganese toxicity was found in a report on manganese grinding workers in Glasgow by Couper et al. in 1837, and extrapyramidal symptoms were subsequently reported in manganese miners in various areas of Europe.

Manganese is an essential element in the body, and 2–9 mg/day is ingested in food. Absorption from the intestine increases in iron, calcium, and magnesium deficiency. Approximately 80% of the manganese in the blood is bound to H2Alg-globulin, and the rest is bound to transferrin and unidentified ligands. It is a constitutive element of metalloproteins, including mitochondrial enzymes, Mn-SOD, pyruvate carboxylase, and glutamine synthetase. Manganese is incorporated by endocytosis mediated by cerebral vascular transferrin receptors, and approximately 80% is localized in astrocytes.

Convulsions are known to occur as a result of manganese deficiency. Decreased manganese content in whole blood has been reported in an epilepsy patient group regardless of whether they were on medication, and it appeared to have been due to a decrease in Mn-SOD and glutamine synthetase activity. Dermatitis, hair damage, and hypocholesterolemia have also been shown to occur. Inner ear damage and ataxia have been mentioned as a result of manganese deficiency during the fetal period in animals.

Toxicity due to excess manganese, in contrast,
causes irreversible psychological manifestations (locura manganica) and neurological manifestations. Pneumonia and bronchitis develop as a result of airway exposure, and excess manganese accumulated in the lungs is said to pass into the brain. Psychological manifestations, such as impaired orientation, memory disorders, compulsive and violent behavior, emotional hypersensitivity, hallucinations, etc., are said to occur in acute poisoning. Progressive neurological manifestations, i.e., akinesia, dystonia, and gait disturbances appear 1–2 months after the onset of mental symptoms, and mask-like facies, articulation disorders, low voice, and monotonous whispering voice develop. In chronic poisoning, symptoms of a nervous breakdown and blunted affect appear after several months to several years of exposure, and progressive akinesia, gait disturbances, language disorders, parkinsonism, dystonia, increased deep tendon reflexes in the lower extremities, excitement, etc., gradually develop.

Neuropathologically, cerebral atrophy, cerebroventricle enlargement, and atrophy of the caudate nucleus, putamen, globus pallidus, and thalamus are observed in manganese poisoning patients, with the greatest damage occurring in the globus pallidus. Loss and demyelination of large neurons in the internal segment of the globus pallidus and astrocyte proliferation are seen, but the substantia nigra is said to be normal. Loss of pigmentation, although mild, is seen in the substantia nigra in chronic manganese poisoning. At the cellular level, manganese accumulation is seen especially at sites in the brain where there is a high content of non-heme iron, the caudate nucleus, putamen, globus pallidus, substantia nigra, and hypothalamic nuclei. Biochemically, there is said to be an increase in dopamine and noradrenaline in the brain in the early stage, and decreases in the late stage. Exogenous manganese is claimed to promote active oxygen production at sites of very active catecholamine metabolism, such as the substantia nigra, and cause cytotoxicity.

Parkinson’s disease and parkinsonism due to manganese exposure clearly differ both in terms of their clinical manifestations and pathological findings, but it has also been shown that environmental factors may be involved in the development of Parkinson’s disease. Air pollution by manganese as a result of the use of methylcyclopentadienyl manganese tricarbonyl (MMT) as an anti-knock compound has recently been demonstrated, and accumulation in the corpus striatum, cerebral cortex, and cerebellum and the development of extrapyramidal manifestations have been shown to occur as a result of administration of MnO2 and MnCl2 via the airway in animal experiments. There has been apprehension about low-concentration manganese content in the air as an environmental factor.8,9)

Aluminum and Neurotoxicity

In 1972 Alfrey et al. noted the onset of articulation disorders, aphasia, convulsions, myoclonus, and dementia symptoms in long-term dialysis patients, and they found high aluminum concentrations in the patients’ brains. Residual aluminum from the hemodialysis process was considered to be the cause, and as a result of removing the aluminum in the dialysis fluid and discontinuing oral administration of aluminum preparations, no new cases have been seen. Although rare, a tendency to have lower scores in neurologic development examinations using the Bayley Mental Development Index has been reported for premature infants and children who have received aluminum-contaminating high-calorie infusion therapy,10) and aluminum has been shown to be replaced by amino acids and to leak out in solutions stored in glassware.

Aluminum encephalopathy has been reported after oral administration of aluminum preparations to chronic renal failure patients. The serum aluminum concentration has been shown to increase to twice the normal upper limit as a result of intravenous alimentation even when
renal function is normal,\textsuperscript{11} and there have also been reports of the occurrence of language disorders, consciousness disorders, or dementia after long-term occupational exposure, such as among workers in an aluminum refinery, an aluminum pot factory, etc. Similar manifestations have been observed as a result of ear-nose-throat (ENT) surgery in which aluminum-containing bone cement (Ionocap\textsuperscript{\textregistered}, Ionocem\textsuperscript{\textregistered}, Ionos GmbH \& Co. KG, Seefeld, Germany) was used. This is thought to represent aluminum poisoning as a result of aluminum coming into direct contact with cerebrospinal fluid and eluted because aluminum-containing cement had been used at bone defect sites or because of accidental entry into the spinal fluid compartment after local CNS fistula formation or surgery.\textsuperscript{12}

**Conclusion**

Associations between aluminum, iron, and manganese have been primarily outlined, where deficiencies and excesses are thought to cause irreversible changes in the nervous system as well as neurodegenerative diseases, notably Alzheimer’s disease, amyotrophic lateral sclerosis, and parkinsonism. These neurodegenerative diseases are suspected of having a multifactorial etiology and of being caused by environmental factors in addition to genetic factors. Although these trace element abnormalities are not thought to exert pathogenetic effects, the evidence suggests that they are involved as risk factors.

**REFERENCES**


