Alzheimer’s Disease and Brain Mineral Metabolism

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Dementia constitutes one of the greatest medical and social problems facing the aging populations of developed countries. Alzheimer’s disease is the main cause of dementia in the elderly, and the cognitive decline that characterizes this disorder clinically is accompanied by the development of hallmark neuropathological changes, including loss of neurons and synapses and the development of senile plaques and neurofibrillary tangles. Plaques consist of extracellular deposits of an abnormal protein fragment, the β-amyloid peptide, which aggregates in fibrils in a “star-burst” array to form the core of mature plaques. This plaque core is surrounded by neuritic processes and glial cells and there is loss of synapses in the adjacent neuropil (1).

Neurofibrillary tangles are lesions in which paired helical filaments (PHFs) are deposited intracellularly. A major component of PHFs is an abnormally phosphorylated form of the microtubule-associated protein, tau, indicating a derangement of cytoskeletal function in affected neurons (2).

THE ETIOPATHOGENESIS OF ALZHEIMER’S DISEASE

It seems likely that Alzheimer’s disease has a complex etiology and that, in common with many other disorders, both genetic and environmental factors may be important. Genetic linkage studies have provided evidence of heterogeneity and some presenile familial forms show linkage to chromosome 21, while others do not (3). A rare familial form involves a base substitution in the gene encoding the β-amyloid precursor protein (APP) located on chromosome 21 (4). However, the majority of late onset cases of Alzheimer’s disease appear to be sporadic and it seems likely that environmental factors are important in this condition.

Environmental agents, including nutritional factors, could in theory contribute to the development of Alzheimer’s disease in two main ways. According to the “threshold model” of neurodegenerative disorders (5), there is an age-related general attrition of neuronal systems with loss of functional capacity, due to the combined effects of genetic and environmental factors. Superimposed on this decline, a more
specific disease process causes accelerated neuronal cell death or dysfunction until the threshold for adaptive compensation is exceeded and clinical symptoms develop. This is illustrated in Fig. 1, which shows age-related changes in the hippocampal content of choline acetyltransferase (ChAT), the enzyme responsible for acetylcholine synthesis, in intellectually normal individuals. Memory loss, a core clinical symptom of Alzheimer’s disease, correlates well with the severe decline in ChAT and other markers of cholinergic function in the hippocampus and neocortex (6). Figure 1 also shows levels of ChAT in patients with Alzheimer’s disease and it is evident that the later the onset of the disorder, the less the levels of ChAT are reduced. This pattern is consistent with the threshold model, the disease in older subjects being expressed against a greater burden of general involutional change, resulting in clinical symptoms with a correspondingly smaller deficit in cholinergic function. A growing body of evidence suggests that alterations in brain mineral homeostasis may play a role in the development of Alzheimer’s disease and a key issue is whether these changes account for part of the general age-related attrition of brain function or whether they contribute more specifically to the etiopathogenesis of the disorder.

THE ROLE OF ALUMINUM

Involvement of aluminum in the etiopathogenesis of Alzheimer’s disease is suggested by several lines of evidence. Aluminum is associated with both of the
characteristic neuropathological lesions, the plaques and tangles. The Al content of
tangle-bearing neurons is increased compared to that of adjacent non-tangled neurons
(7). Studies in susceptible animal species have shown that Al induces the abnormal
phosphorylation of neurofilament proteins (8), an aberration similar to that which
occurs in the hyperphosphorylated form of tau associated with PHFs in Alzheimer’s
disease (2). Aluminum in the form of amorphous aluminosilicate is present at the
center of the β-amyloid core in mature senile plaques (9,10) and such deposits have
not been found associated with other neuropathological lesions or systemic amyloid
deposits (11). Although these changes have not been consistently found by some
other groups, we have argued that this is probably due to methodological problems
and have confirmed the presence of Al in plaque cores using a variety of techniques
including both energy and wavelength dispersive scanning electron microprobe x-
ray analysis, scanning proton microprobe x-ray microanalysis, and imaging second-
ary ion mass spectrometry (SIMS).

Aluminum in the circulation is mainly, if not completely, bound to the iron-trans-
porting protein transferrin and entry to the brain appears to be largely via this route
(12,13). Accumulation of Al occurs in regions of the brain that contain high densities
of transferrin receptors, notably in regions such as cortex, hippocampus, and amygd-
ala, which are selectively vulnerable in Alzheimer’s disease.

Immunocytochemical staining for the transferrin receptor reveals high densities
on pyramidal cells and other projection neurons that have the greatest requirement
for iron in the synthesis of respiratory chain enzymes. Studies using imaging SIMS
have shown high focal concentrations of Al with a laminar distribution corresponding
to that of pyramidal neurons in the brains of patients with chronic renal failure (13).
Such patients are exposed to high plasma levels of Al as a consequence of impaired
renal excretion and chronic treatment with Al-containing phosphate binders to pre-
vent hyperphosphatemia. Figure 2 illustrates the finding that cortical pyramidal neu-
rons in dialysis patients show increased staining for the β-APP and also that ap-
proximately 30% of these patients exhibit precocious deposition of β-amyloid in the
form of immature plaques (14). Although APP may be a “cell stress” protein, such
changes have not been found in patients with hepatic encephalopathy, and β-amyloid
deposition may thus be a direct response to the accumulation of toxic levels of Al
in these cells.

Aluminum causes dialysis encephalopathy (15) and although the neuropathological
changes in this condition do not resemble those in Alzheimer’s disease, this probably
reflects the severity and relatively acute form of exposure. The deposition of β-
amyloid during senile plaque formation appears to occur over years and probably
even decades (16), a time course consistent with the slow accumulation of aluminum
in vulnerable neuronal populations that could lead to pathological changes including
the increased expression or abnormal processing of APP. We have shown that the
incidence of presenile Alzheimer’s disease appears to be increased in areas where
there are high levels of aluminum in water supplies (17) and similar findings have
been reported from three other studies (18–20). This relationship is surprising in
view of the relatively small proportion of dietary Al contributed by water, compared
with the much larger amounts from other sources including food additives, medicines, and substances such as tea, which are naturally rich in aluminum (21). One possible explanation is that the soluble forms of Al that result from water treatment may represent a particularly bioavailable source. However, Birchall has pointed out an alternative explanation that focuses on the important role of silicon in relation to aluminum toxicity.

THE ROLE OF SILICON IN ALUMINUM TOXICITY

Unlike aluminum, silicon appears to be an essential trace element and Birchall and Chappell have proposed that its main role in the body may be to limit the bioavailability of aluminum (22). They have also suggested that the epidemiological findings referred to above may be explained by the broad inverse relationship that exists between the content of Al and Si in water supplies and the ability of silicic acid, Si(OH)₄, the dissolved form of Si, to complex with Al³⁺ from other dietary sources and thus reduce the general bioavailability of aluminum (23). Silicon is present in serum as silicic acid and it is also present in cerebrospinal fluid (24). The solubility of Si(OH)₄ decreases markedly in the presence of Al, and aluminosilicate complexes can form at extracellular pH (22). Thus, high focal concentrations of Al released on neuronal cell death may complex with Si(OH)₄ in the extracellular fluid to form a focal deposit of aluminosilicate that could act as a nidus for plaque core formation. A significant increase in the cerebrospinal fluid content of Si in senile but not presenile Alzheimer's disease has been reported, and this correlated with the severity of functional impairment (24). This increase may reflect the accumulation of aluminum and development of core-containing senile plaques in which aluminosilicate deposits are present (9,10).
CALCITONIN HOMEOGSTASIS IN DEMENTIA

Altered cellular calcium homeostasis has been reported in Alzheimer's disease and could potentially contribute to neurodegenerative changes through effects such as those on cytoskeletal turnover and excitatory amino acid–mediated neurotoxicity. It has been proposed that the parkinsonism–dementia–ALS complex of Guam represents a form of secondary hyperparathyroidism due to chronic deficiency of calcium and magnesium, which results in increased accumulation of toxic metal ions in the nervous system (25). The prevalence and severity of calcification of the basal ganglia are greater in Down syndrome and in patients under 75 years of age with Alzheimer's disease, in comparison with age-matched controls. Cellular calcium content increases with age and is significantly elevated in the cortex of neuropathologically confirmed cases of Alzheimer's disease (26). There is evidence that changes in cellular calcium homeostasis may be present in peripheral tissue in Alzheimer's disease and reduced calcium uptake in vitro by skin fibroblasts and mitogen-stimulated lymphocytes has been reported. Using 45Ca, we have recently shown that there is a marked decrease in the gastrointestinal absorption of calcium in Alzheimer patients and that this occurs in the presence of normal plasma concentrations of parathormone and vitamin D metabolites (27). However, similar changes were also found in patients with multi-infarct dementia, suggesting that this impairment is a non-specific derangement (Table 1). Furthermore, in an epidemiological study to determine whether the negative calcium balance of age-related osteoporosis predisposed to senile dementia, we have measured bone mass and cognitive function in elderly hip fracture patients (28). No correlation was evident between mental test score and bone mass in the proximal femur measured in 347 patients (Fig. 3). The results are consistent with the view that dementia is associated with an increased

<table>
<thead>
<tr>
<th>Group</th>
<th>Alzheimer's disease</th>
<th>Multi-infarct dementia</th>
<th>Controls</th>
</tr>
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<tbody>
<tr>
<td>No.</td>
<td>26</td>
<td>11</td>
<td>24</td>
</tr>
<tr>
<td>Age</td>
<td>76 ± 7</td>
<td>76 ± 9</td>
<td>74 ± 5</td>
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<tr>
<td>Mental test score</td>
<td>9***</td>
<td>11***</td>
<td>26</td>
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<tr>
<td>Serum Ca (mmol/liter)</td>
<td>2.43 ± 0.13</td>
<td>2.35 ± 0.08</td>
<td>2.45 ± 0.1</td>
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<tr>
<td>Serum PTH (ng/ml)</td>
<td>0.8 ± 0.5</td>
<td>—</td>
<td>0.8 ± 0.3</td>
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<tr>
<td>1,25(OH)2 vitamin D (pg/ml)</td>
<td>22 ± 12</td>
<td>—</td>
<td>20 ± 8</td>
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<tr>
<td>45Ca absorption</td>
<td>0.29 ± 0.17**</td>
<td>0.38 ± 0.24*</td>
<td>0.6 ± 0.3</td>
</tr>
</tbody>
</table>

Absorption of radioactive calcium in Alzheimer's disease, multi-infarct dementia, and age-matched control subjects, measured using a method that takes weight into account and correlates well with dual isotope and metabolic balance studies (24). Reduced absorption of 45Ca in Alzheimer's disease occurs in the presence of normal levels of parathormone and vitamin D metabolites. Means ± SD. * p < 0.05; ** p < 0.01; *** p < 0.001.
FIG. 3. Relationship between bone mass and cognitive function in the elderly: Bone mass of the proximal femur in 78 hip fracture patients with severe dementia and 123 intellectually normal fracture patients, showing similar pattern of distribution. The Singh grade is a measure of femoral neck trabecular pattern from grade 6, where all major trabeculae are present, to grade 1 in which only the primary compressive group is visible. A further 146 patients with mild to moderate dementia showed a similar pattern of distribution.

risk of falling rather than with any complex etiopathological hypothesis linking negative calcium balance, as evidenced by osteoporosis, with dementia in the elderly. These findings do not, of course, exclude the possibility that derangements of neuronal calcium homeostasis could have an important role in the development of degenerative changes associated with dementia.

IMPLICATIONS FOR NUTRITIONAL RESEARCH

Understanding the changes in brain mineral homeostasis that occur during brain aging and in dementing disorders is a major challenge for future research. This brief chapter has focused on the possible neurotoxic actions of aluminum accumulation in the nervous system, the poorly understood role of silicon in relation to aluminum toxicity, and age-related changes in calcium homeostasis. Alterations in the neuronal homeostasis of other elements such as iron, manganese, and zinc may be of equal importance and are also poorly understood. The potential of iron to promote hydroxyl ion free-radical formation and cell damage by lipid peroxidation in disorders such as Alzheimer’s disease and Parkinson’s disease is an important area for research. It is of interest that the first genetic mutation to be described for familial Alzheimer’s disease (4) may involve disruption of a regulatory stem-loop structure in the messenger RNA for the β-APP (29). This stem-loop contains the consensus nucleotide sequence found in the iron-responsive elements in the genes that encode for ferritin and the transferrin receptor and, by analogy, may be a translational reg-
ulatory site that controls production of APP. If the synthesis of this key protein in Alzheimer-type pathology is regulated in some way by intracellular iron homeostasis, such a mechanism could provide a unifying hypothesis for the role of genetic and environmental factors in the etiopathogenesis of this disorder.

The evidence suggesting that aluminum may contribute to age-related neurodegenerative changes raises obvious questions for investigation. Whereas some dietary constituents, such as citrate, markedly enhance the gastrointestinal absorption of aluminum, others, such as phosphate, fluoride, polyphenolic organic groups, and silicic acid, may interact with Al to reduce absorption. It remains to be determined whether intervention through chelation therapy or the increased intake of Si(OH)₄, for example, will significantly decrease Al absorption and slow the progression of Alzheimer’s disease. There may be age-related changes in the uptake, tissue distribution, and excretion of Al, and genetic or other constitutional factors that confer susceptibility in some individuals. A pilot study from this laboratory has indicated that Alzheimer patients below the age of 75 years show increased absorption of Al following an oral challenge with aluminum citrate compared with age-matched controls, whereas other work has suggested that the binding of ⁶⁷Ga (and by implication Al) to plasma transferrin may be altered in Alzheimer’s disease and Down syndrome (30). The apparent lack of a correlation between bone mass and dementia (28) suggests that there is no direct relationship between the negative calcium balance of old age and the processes that underlie dementia, but cognitive studies in large cohorts of subjects treated to prevent osteoporosis may shed further light on this problem. The possibility that age-related increases in free-radical-mediated damage or APP gene expression may result from alterations in neuronal iron homeostasis is another key issue, since such mechanisms could, ultimately, afford the possibility of control via pharmacological and nutritional strategies.

REFERENCES

10. Edwardson JA, Klinowski J, Oakley AE, Perry RH, Candy JM. Aluminosilicates and the aging brain:

DISCUSSION

Dr. Schiffman: One of the major theories about the entry of aluminum into the brain is that it occurs via the nasal mucosa. What is your view on this?

Dr. Edwardson: I would disagree about this being a major hypothesis for the entry of aluminum into the brain. As far as I am aware, this is a minority view. The experimental studies that have shown translocation of aluminum in various forms from the nasal epithelium into the brain have been experimental situations in which vast quantities of aluminum have been applied directly to the nasal epithelium. We have looked at the uptake of aluminum in the brains of renal dialysis patients using imaging secondary iron mass spectrometry and it is quite clear that one can see increased focal accumulation of aluminum in many areas, including the olfactory system. This suggests that the primary route of access of aluminum,
even in olfactory structures, is probably via transferrin-mediated transport from the circulation rather than by direct inhalation and transport from the nasal mucosa.

**Dr. Schiffman:** If aluminum is absorbed into the blood stream, why should it be specifically concentrated in the olfactory areas?

**Dr. Edwardson:** Because the neurons in those areas, like those in other regions such as the cortex and hippocampus, which selectively accumulate aluminum, appear to be very active metabolically and have very high densities of transferrin receptors.

**Dr. Schiffman:** Many of our Alzheimer patients have worked in an aluminum-contaminated environment. This is what makes me wonder whether the nasal route is a possibility.

**Dr. Edwardson:** I agree this should not be ruled out. An important study that may be relevant to this subject was that of Sandra Rifat and her colleagues from Toronto (1). They looked at cognitive impairment in a large group of miners who were deliberately exposed to the inhalation of finely divided aluminum and aluminum oxide to prevent silicosis. They showed clear evidence of cognitive decline in this group and a graded response dependent on the duration of exposure. However, the Toronto group were unable to identify the route of entry of aluminum. It could have got in through the nasal mucosa, but it could also have been swallowed in mucus from the respiratory system and absorbed through the gastrointestinal tract.

**Dr. Steen:** There is surprisingly similar prevalence of dementia the world over, irrespective of exogenous factors. What range is there in aluminum concentration in the water in different parts of the world?

**Dr. Edwardson:** I wouldn’t suggest for a moment that aluminum is the major environmental risk factor for Alzheimer’s disease. It is probably just one among a range of others. Although rates of dementia appear to be relatively uniform globally, neuropathological studies have shown that there is considerable variation in the proportion of patients suffering from multi-infarct dementia compared to Alzheimer’s disease, the former being markedly increased in Japan, for example. Overall, Alzheimer’s disease accounts for about 50% of all cases of dementia. As far as aluminum in water is concerned, this varies from less than 5 parts per billion in some hard water areas, to 1,000 to 2,000 parts per billion in areas where aluminum treatment is used to remove humic acid and other organic acids. The maximum permitted concentration in the European Community is 200 parts per billion, but this value is set on practical grounds rather than for any reasons of safety. One possible explanation for the epidemiological data is that it is not the concentration of aluminum that is important but rather the level of silicon, which can vary from 0.5 up to 150 mg per liter.

**Dr. Guesry:** Is it true that silicon is more abundant in water coming from granitic areas such as Brittany, Cornwall, Scotland, and Ireland? Do you have any information on the rate of Alzheimer’s disease in these parts of the world?

**Dr. Edwardson:** As far as I am aware, granitic rocks are notably resistant to weathering. The very soft waters from these areas cause considerable problems for the water industry because of the content of organic acids, which cause discoloration, and it is these waters particularly that are treated with aluminum. There is much less silicon in these soft waters compared to the amounts present in hard water from the sedimentary rocks. In fact, silicon is often the major solute component of hard water and overall it correlates better with magnesium and calcium than with aluminum.

**Dr. Davies:** I believe that aluminum-containing antacids are often prescribed for the elderly. Could this be a dangerous prescription in relation to the risk of Alzheimer’s disease?

**Dr. Edwardson:** On the available evidence, it is difficult to say. The question has been examined in a number of epidemiological studies, two of which were large enough to provide
adequate data. In one of these no association was found (2); in the other (3), an association was found but it broke down when the analysis examined whether the antacids contained aluminum or not. There is a major problem of informant reliability in retrospective studies and a prospective study is needed. Aluminum absorption is strongly facilitated by acidic conditions and since the prime purpose of giving antacids is to increase gastric pH, the amounts of aluminum absorbed are not nearly so great as one might imagine on the basis of the aluminum ingested. The vast majority of aluminum taken in antacids is simply not absorbed. There is, however, evidence of increased aluminum deposition in bone and soft tissues in people who have taken aluminum-containing antacids over a period of years.

REFERENCES