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Status of Aluminum as a Risk Factor for Dialysis Encephalopathy and Alzheimer's Disease

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Editorial

Status of aluminum as a risk factor for dialysis encephalopathy and Alzheimer's disease

Dialysis encephalopathy and Alzheimer's disease (AD) are important causes of dementia. The search for environmental risk factors has produced provocative clues linking aluminum to the pathogenesis of both conditions (1-10). Aluminum, abundant in vegetable and animal tissues, untreated water, foods, fluids, and medications (11, 12), accumulates in bone, brain, and other tissues in renal failure and may be associated with toxic manifestations including dementia (1-5). Beyond renal failure, there is evidence that aluminum may also be important in the pathogenesis of AD (6-10). We review the salient features of the controversy about the role of aluminum in dialysis encephalopathy and AD (13-18).

Dialysis encephalopathy

First described in the early 1970s, is a frequently fatal syndrome of dementia, mixed dysarthria-apraxia of speech, asterixis, myoclonus and focal seizures (1-4). EEG shows generalized slowing, multifocal bursts of delta activity and spikes. The syndrome was linked to absorption of aluminum from phosphate binding gels or the dialysate. Most patients received hemodialysis for about 3 to 7 years before onset of symptoms. Aluminum toxicity may also cause bone disease and anemia.

In the epidemic form of dialysis encephalopathy lowering dialysate aluminum levels prevented the occurence of new cases (2, 19). Some patients reportedly improved after treatment with desferoxamine (19), a heavy-metal chelator.

Patients with dialysis-associated encephalopathy showed markedly elevated brain gray-matter aluminum compared to controls or dialysis patients dying from other causes (1). Furthermore, brain gray-matter aluminum levels vary directly with the duration of dialysis, and there may be neurofibrillary tangles (NFTs) and senile plaques (SPs) similar to those in AD. Thus clinical and pathological evidence suggests an association between aluminum and dialysis encephalopathy.

The role of aluminum in the pathogenesis of dialysis encephalopathy, however, has not gone unchalleged (19). It is argued that brain histopathology in dialysis encephalopathy is non-specific, and that some patients have essentially normal brain necropsy findings (3). Other pathophysiologic mechanisms have been suggested: normal pressure hydrocephalus, regional cerebral blood flow alterations, cerebral atrophy, slow virus infection, or other potential neurotoxic elements (e.g. cadmium, mercury, nickel, manganese, thallium, or boron) (19). Brain aluminum may also be elevated in patients with metastatic cancer, hepatic coma, or in those more than 60 years old. Thus, it has been suggested that dialysis encephalopathy may be of multifactorial etiology with different disease processes converging to a common clinical presentation (3).

Alzheimer's disease

The leading cause of dementia among the elderly, (20) afflicts over 2 million Americans. Demographic projections suggest that by the year 2050 there may be over 8.5 million AD patients in the U.S. (21). While policy makers ponder innovative strategies to keep pace with the epidemic, epidemiologists and experimentalists search for risk factors and preventive strategies. Epidemiologic studies have consistently pointed to advanced age as a risk factor (20), and studies of familial AD, Down's syndrome and the molecular biology of amyloid all suggest a genetic link to chromosome 21 (22).

The major histopathologic features of AD are neur-

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onal loss, dystrophic nerve fibers, reduction in arborization of dendrites, NFTs, SPs, granulovacuolar degeneration, Hirano bodies, vascular amyloid, and lipofuscin storage (23). These changes are non specific and may be observed in normal aging but are more intense in AD and have a different neuroanatomical distribution. For example, in aging, NFTs occur mainly in the hippocampus, parahippocampal gyrus, amygdala, cholinergic basal magnocellular complex, and monoaminergic nuclei of the brainstem. SPs are found in the same above-mentioned cortical areas, the neocortex, and the amygdala. In contradistinction, in AD the density of NFTs and SPs is markedly increased, involving the neocortex primarily in association areas and sparing primary cortical areas.

NFTs and SPs are considered neuropathologic hallmarks of AD. NFTs belong to the amyloid class of proteins or glycoproteins. Electron microscopy demonstrates paired helical filaments (PHFs). Tau, a microtubule protein, and ubiquitin, a putative protein marker signaling degeneration, been identified in NFTs. SPs on the other hand contain degenerating cell processes of astrocytes and possibly microglial cells, and frequently surround an extracellular amyloid core containing β protein, the gene for which has been localized to chromosome 21. Alz-50, a monoclonal antibody, reacts positively with virtually every neurite in plaques of AD patients and may serve as a useful diagnostic marker (24). How then might aluminum play a role in the pathogenesis of AD?

Neuropathologic evidence linking aluminum to AD was reported in the 1970s and 1980s (13). Elevated aluminum concentrations in the cerebral cortex of patients with AD were confirmed in independent laboratories using different elemental analytic techniques. The principle loci of aluminum accumulation in AD affected tissues are DNA structures of the nucleus, protein moieties of NFTs, amyloid cores of SPs (aluminosilicate complexes), and cerebral ferritin. Aluminum has been associated with deleterious cellular events, including adverse effects on the DNA transcription process, formation of PHFs, accelerated peroxidation of membrane lipids stimulated by iron salts, and disturbed intracellular regulation of calcium and calcium dependent electrophysiologic functions. Exactly how aluminum gains access to the neuron is unknown. It has been hypothesized that a defective blood-brain-barrier and "leaky" neuronal membrane underlie a genetically mediated process of aluminum accumulation and exclusion (aluminum tolerance gene hypothesis) (13).

Whether aluminum passively accumulates in neurons as an epiphenomenon or is a true neurotoxin causing AD remains controversial. Skeptics on the pathophysiologic link between aluminum and AD have leveled substantial criticism (14, 18): **a)** findings of elevated brain aluminum in patients with AD are not consistent, nor are aluminosilicate deposition in SPs; **b)** there are significant differences in cellular topography, morphology and location of NFTs between those experimentally-induced by aluminum and those of AD patients; **c)** no obvious differences have been observed in protein synthesis by free membrane bound polyribosomes in a cell-free system from control and aluminum-treated rabbits; **d)** some aluminum experimental studies have shown no significant change in the cholinergic system, a major target of dysfunction in AD; and **e)** significant differences exist between the clinical and laboratory phenomenon observed in aluminum associated dialysis encephalopathy and AD (e.g., absolute brain aluminum levels, total body aluminum stores, response to chelation therapy, and associated aluminum-linked disease). Overall, doubters have argued that the evidence linking neurologic toxicity to aluminum is far more compelling than that directly linking aluminum to the pathogenesis of AD.

As the precise mechanism mediating the transport and accumulation of aluminum and the primary site of aluminum neurotoxicity are unknown (17), there remain several unresolved questions about the role of aluminum in AD (16): **a)** is aluminum increased in neurons with normal morphology that are apparently physiologically intact? **b)** is a condensation of intermediate euchromatin possibly altering transcriptional activity? **c)** does the physical structure of heterochromatin containing neurons differ in AD from those of normal age-matched controls? **(d)** does aluminum affect the mitochondrial genome? and **(e)** what is the intracellular carrier/transport system by which aluminum gains entry into the neuron? Answers to these questions could clarify the aluminum-AD and aluminum-dialysis encephalopathy controversy.

The evidence for a primary role for aluminum in the pathogenesis of dialysis encephalopathy is compelling. The argument linking aluminum to AD

is provocative but so far inconclusive. Recent evidence implicating aluminum in the down regulation of transcription of neuron specific genes through increased electrostatic binding of proteins, particularly the methionine containing histone H1, to DNA (25), and epidemiologic evidence of an increase in AD in areas with higher concentrations of aluminum in the drinking water (26, 27) warrant further research. Studies focusing on the mechanism of transport and accumulation of aluminum in the brain, its primary site of action, and the role of chelation therapy (28) hold promise.

Possibly dialysis encephalopathy and AD will be shown in the future to be linked by the presence of β_2-microglobulin as a marker or pathophysiologic link for enhanced aluminum trapping in the brain (29, 30); or an abnormality of transferrin binding in AD and saturation of the normal transferin binding mechanism by excessive aluminum loads in dialysis encephalopathy-resulting in increased deposition of aluminum in the brain in both conditions (31).

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REFERENCES

1. Alfrey AC, LeGendre GR, Kaehny WD. The dialysis encephalopathy syndrome. Possible aluminum intoxication. N Engl J Med 1976; 294: 184-8.
2. Dunea G, Mahurkar SD, Mamdani B, Smith EC. Role of aluminum in dialysis dementia. Ann Intern Med 1978; 88: 502-4.
3. Arieff AL, Cooper JD, Armstrong D, Lazarowitz VC. Dementia, renal failure and brain aluminum. Ann Intern Med 1979; 90: 741-7.
4. Alfrey AC. Dialysis encephalopathy. Kidney Int 1986 (suppl 18); 29: S53-7.
5. Milne FJ, Sharfe B, Bell P, Meyers AM. The effect of low aluminum water and desferrioxamine on the outcome of dialysis encephalopathy. Clin Nephrol 1983; 20: 202-7.
6. Crapper DR, Krishnan SS, Dalton AJ. Brain aluminum distribution in Alzheimer's disease and experimental neurofibrillary degeneration. Science 1973; 180: 511-3.
7. Crapper DR, Krishnan SS, Quittkat S. Aluminum, neurofibrillary degeneration and Alzheimer's disease. Brain 1976; 99: 67-80.
8. Crapper DR, Quittkat S, Krishnan SS, et al. Intranuclear aluminum content in Alzheimer's disease, dialysis encephalopathy and experimental aluminum encephalopathy. Acta Neuropathol (Berl) 1980; 50: 19-24.
9. McDermott JR, Smith AI, Iqbal K, Wisniewski HM. Brain aluminum in aging and Alzheimer disease. Neurology 1979; 29: 809-14.
10. Wisniewski HM, Sturman JA, Shek JW. Aluminum chloride induced neurofibrillary changes in the developing rabbit: a chronic animal model. Ann Neurol 1980; 8: 479-90.

11. Crapper DR, DeBoni U. Aluminum. In: Spencer PS, Schaumburg HH, eds. Experimental and clinical neurotoxicology. Baltimore: Williams and Wilkins, 1980; 326-35.
12. Wills MR, Savory J. Aluminum and chronic renal failure: sources, absorption, transport and toxicity. CRC Crit Rev Clin Lab Sci 1989; 27(1): 59-107.
13. Mclachlan DRC. Aluminum and Alzheimer's disease. Neurobiology of Aging 1986; 7: 525-32.
14. Wisniewski HM, Mortez RC, Iqbal K. No evidence for aluminum in etiology and pathogenesis of Alzheimer's disease. Neurobiology of Aging 1986; 7: 532-5.
15. Khachaturian ZS. Aluminum toxicity among other views on the etiology of Alzheimer's disease. Neurobiology of Aging 1986; 7: 537-9.
16. Pettegrew JW. Aluminum and Alzheimer's disease: an evolving understanding. Neurobiology of Aging 1986; 7: 539-4.
17. Jope RS. Aluminum toxicity. Transport and sites of action. Neurobiology of Aging 1986; 7: 541-2.
18. Alfrey AC. Systemic toxicity of aluminum in man. Neurobiology of Aging 1986; 7: 543-5.
19. Fraser CL, Arieff AL. Nervous system complications in uremia. Annals of Internal Medicine 1988; 109: 143-53.
20. Brody JA, Cohen D. Epidemiologic aspects of Alzheimer's disease. Facts and fragments. Journal of Aging and Health 1989; 1(2): 139-49.
21. Roth M. Some strategies for tackling the problems of senile dementia and related disorders within the next decade. Danish Medical Bulletin 1985; 32 (1); 92-111.
22. Bowen DM, Beyreuther K, Cross AJ, et al. Group report: Cell injury: molecular biology and genetic basis. In: Henderson AS, Henderson JH, eds. Etiology of dementia of Alzheimer's type. New York: John Wiley and Sons, 1988; 165-76.
23. Hauw J-J, Duyckaerts C, Delaère P. Neuropathology of aging and DAT: How can age-related changes be distinguished from those due to disease processes? In: Henderson AS, Henderson JH, eds. Etiology of Dementia of Alzheimer's type. New York: John Wiley and Sons, 1988; 195-211.
24. Davies P. Protein abnormalities in the Alzheimer brain. In: Henderson AS, Henderson JH, eds. Etiology of dementia of Alzheimer's type. New York: John Wiley and Sons, 1988; 135-47.
25. McLachlan DRC, Lukiw WJ, Kruch TPA. New evidence for an active role of aluminum in Alzheimer's disease. Can J Neurol Sci 1989; 16: 490-7.
26. Martyn CN, Osmond C, Edwardson JA, Barker DJP, Harris EC, Lacey RF. Geographical relation between Alzheimer's Disease and aluminum in drinking water. Lancet 1989; 59-62.
27. Vogt T. Water quality and health: study of possible relation between aluminum in drinking water and dementia. Statistisk Sentralbyra (Central Bureau of Statistics of Norway) Oslo-Kongsvinger. ISBN 82-537-2370-9, ISSN 0085-43444, 1986.
28. Kruck TPA, McLachlan DRC. Aluminum as a pathogenic factor in senile dementia of the Alzheimer type: ion specific chelation. Alzheimer Disease and Related Disorders 1989; 1155-67.
29. Selkoe DJ, Abraham CR, Podlisny MB, Duffy LK. Isolation of low-molecular-weight proteins from amyloid plaque fibers in Alzheimer's disease. J Neurochem 1986; 46: 1820-34.
30. Ullian ME, Hammond WS, Alfrey AC, Schultz A, Molitoris BA. β-2-microglobulin-associated amyloidosis in chronic hemodialysis patients with carpal tunnel syndrome. Medicine 1989; 68: 107-15.
31. Farrar G, Altmann P, Welch S, et al. Defective gallium-transferrin binding in Alzheimer disease and Down syndrome: possible mechanisms for accumulation of aluminum in brain. Lancet 1990; 335: 747-50.