Aluminum, Alzheimer's disease and bone fragility

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The incidence of fragility fractures has increased epidemically. Especially patients with senile dementia (including Alzheimer's disease) have a greatly increased risk of fragility fractures. Aluminum inhibits bone mineralization; the greater the aluminium exposure, the higher the risk of an early fracture. Aluminium is neurotoxic and may, in addition to genetic factors, play a role in the development of Alzheimer's disease by contributing to the formation of the characteristic beta-amyloid and neurofibrillary tangles. Thus, a common denominator between Alzheimer's disease and bone fragility may be a chronic low-grade aluminum intoxication. The epidemic of fragility fractures may be caused by increased aluminium exposure—due to the use of aluminum cooking pots or the pollution acidification of our environment.

In our pilot study of 26 hip-fracture patients (13 patients with Alzheimer's disease and 13 individually age- and gender-matched non-demented patients), the aluminum content, determined mass-spectrometrically, was higher in trabecular bone biopsies from the patients with Alzheimer's disease than from the non-demented patients ($p = 0.005$). The aluminum content was also higher in the younger of the 26 patients ($p = 0.02$). Our findings agree with the hypothesis that aluminum plays a role in the development of Alzheimer's disease and bone fragility.

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Alzheimer's disease is neuropathologically characterized by extracellular deposition of beta-amyloid and intraneuronal accumulation of neurofibrillary tangles. Much research has been focused on the etiology and pathogenesis of the disease. The rare early-onset Alzheimer's disease is often associated with mutations in the amyloid precursor protein gene or in the presenilin genes (Scheuner et al. 1996). The common late-onset Alzheimer's disease is more frequent in carriers of the epsilon-4 allele of apolipoprotein E, but often no genetic explanation is found (Lannfelt et al. 1994).

The amyloid hypothesis suggests that a disturbed metabolism of the amyloid precursor protein (leading to an excessive production of beta-amyloid) plays a central role in Alzheimer's disease, though the mechanism of beta-amyloid production is unclear in cases without a mutation in the amyloid precursor protein gene (Scheuner et al. 1996) and the development of the neurofibrillary tangles remains unexplained.

The aluminum hypothesis is controversial (Crapper McLachlan et al. 1989, Doll 1993, Nieboer et al. 1995): Alzheimer's disease has, though not undisputed (Wood et al. 1988, Wettstein et al. 1991, Landsberg et al. 1992), been associated, on the one hand, with aluminum accumulation in the nuclear chromatin (Crapper et al. 1980, Good et al. 1992), in the neurofibrillary tangles (Perl and Brody 1980, Good et al. 1992) and focally in specific regions of the brain (Xu et al. 1992) and, on the other hand, with aluminum in drinking water (Flaten 1986, Vogt 1986, Martyn et al. 1989, Flaten 1990, Frecker 1991, Crapper McLachlan et al. 1996).

Aluminum dissolves in an acid environment and can be resorbed in the intestine, especially after complexing with organic acids (Slanina et al. 1986). The aluminum absorption varies largely between individuals, increases with age and is raised in young patients with Alzheimer's disease (Taylor et al. 1992). Most resorbed aluminum is excreted; the non-excreted part is largely deposited in bone. Some resorbed aluminium leaks slowly into the cells and may interfere with the transcription of DNA (Lukiw et al. 1992), increase the production of beta-amyloid from the amyloid precursor protein (Clauberg and Joshi 1993, Zatta et al. 1993), induce aggregation of the beta-amyloid (Mantyh et al. 1993, Kawahara et al. 1994, Exley et al. 1995) and contribute to the formation of neurofibrillary tangles (Shin et al. 1995, Zatta 1995).

The fragility of bone in the elderly has been associated with decreased bone mineral content, the cause

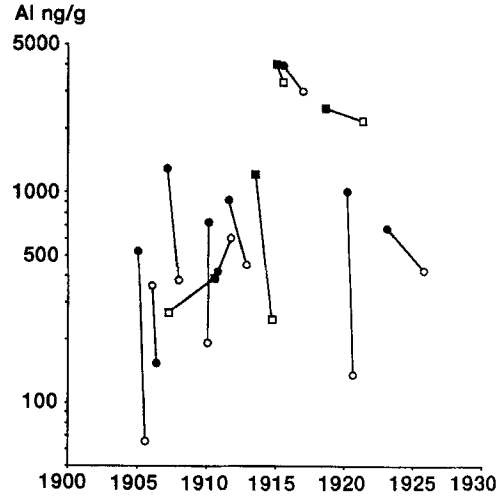
of which is not known. The debate has focused on estrogens, body weight, calcium, phosphorus and vitamin D intake, physical activity, alcoholism, cigarette smoking, medications and medical disorders (Cummings et al. 1985). Patients with senile dementia (including Alzheimer's disease) have an increased risk of fragility fractures (Leitch et al. 1964, Hansson et al. 1982), e.g., a 7–12 times greater risk of hip fracture than the general population (Hansson et al. 1982). Aluminum inhibits bone mineralization (Rodriguez et al. 1990, Zhu et al. 1990). Thus, aluminum may play a role in the development of Alzheimer's disease and bone fragility (Mjöberg 1990).

The accelerated pollution acidification in industrialized countries since the 1950s has led to one of the greatest ecological changes in historical times. An expression of this is the extensive forest decline in Central Europe. Aluminum is normally almost insoluble, but it dissolves in an acid environment and becomes toxic to both plants and animals. Aluminum is a major factor limiting plant growth on acid soils, produced more or less naturally or by acid rain (Delhaize and Ryan 1995). Pied flycatchers breeding close to acidified lakes, and thus feeding on aluminum-containing insects, produce eggs with defective mineralization of the shells because of aluminum intoxication (Nyholm 1981).

During these last 5 decades, the age-specific incidence of hip fracture has increased epidemically. The epidemic of fragility fractures may be caused by an increased long-term aluminum exposure due to frequent stewing of acidic fruits in aluminum pots or the acidification of our environment (Mjöberg 1990). The former suggestion is supported by a recent case-control study (Cumming and Klineberg 1994), and the latter by the apparent association between high levels of aluminum in drinking water (Flaten 1986, Vogt 1986, Flaten 1990) and the very high incidence of hip fractures in Norway (Falch et al. 1985).

Pilot study

Biopsies were taken from the trabecular bone in the trochanter major at operation of 120 patients for hip fracture during 1990–1993. The bone samples were immediately put in sealed polyethylene test tubes, frozen and stored at –20 °C until analysis. 13 patients (9 women) born 1905–1923 (mean age 79 years) had the clinical diagnosis (DSM-IIIR criteria) of Alzheimer's disease (senile dementia of the Alzheimer type). From the remaining patients, an individually age- and gender-matched mentally alert control group of 13 patients (mean age 78 years) was selected. The median age differences between the pairs was 0.8 (range –3.3 to 3.0) years. The 26 bone samples were weighed, decomposed using ultra-pure nitric acid in a quartz tube, diluted with high purity water (with a resistivity of more than 18 MΩ-cm), introduced into an inductively coupled plasma mass-spectrometer and measured for their content of aluminium. All handling of the samples was done in a clean room. Quality control was assessed by the use of a certified reference material (IAEA H-8 Animal bone) in every fifth sample.



Bone aluminum content in 13 hip-fracture patients with Alzheimer's disease (■ = male and ● = female) compared with 13 individually age- and gender-matched non-demented hip-fracture patients (□ = male and ○ = female).

All 26 specimens contained aluminum: the aluminium content varied between 66 and 4080 ng/g wet bone (Figure). There was a higher aluminum content in patients with Alzheimer's disease ($p = 0.005$; Wilcoxon signed rank test) and in the younger of the 26 hip-fracture patients ($p = 0.02$; Spearman rank correlation). 6 patients (3 with Alzheimer's disease and 3 non-demented controls) born 1915–1921 had a relatively high aluminum content (2200–4080 ng/g).

Comments

That a high-grade aluminum intoxication inhibits bone mineralization has been known for decades. Our findings agree with the hypothesis that a chronic low-grade aluminum intoxication plays a role in the development not only of Alzheimer's disease but also of

bone fragility: the greater the aluminum exposure, the higher the risk of an early fracture. This would explain the higher aluminum content in younger hip-fracture patients in our study—otherwise unexpected because aluminum absorption increases with age (Taylor et al. 1992)—as well as the increased risk of fragility fractures in patients with Alzheimer's disease (Leitch et al. 1964, Hansson et al. 1982). However, the relationship between aluminum accumulation (as measured in the bone) and Alzheimer's disease cannot be a simple one, as not all cases with high aluminum content result in Alzheimer's disease (Figure). The variability in aluminum neurotoxicity may be due to individual differences in the permeability of the blood brain barrier (Fosmire et al. 1993).

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