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Invited review

Aluminum toxicity in childhood

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Abstract. Aluminum intoxication is an iatrogenic disease caused by the use of aluminum compounds for phosphate binding and by the contamination of parenteral fluids. Although organ aluminum deposition was noted as early as 1880 and toxicity was documented in the 1960s, the inability to accurately measure serum and tissue aluminum prevented delineation of its toxic effects until the 1970s. Aluminum toxicity has now been conclusively shown to cause encephalopathy, metabolic bone disease, and microcytic anemia.

Key words: Aluminum – Childhood renal failure – Encephalopathy – Osteomalacia – Microcytic anemia – Aluminum-containing antacids

Introduction

Aluminum toxicity has been proven through extensive epidemiological studies in adult dialysis patients and by reproducing the disease in animals. These studies have documented that encephalopathy, bone disease, and anemia can occur during exposure to high-dose aluminum and resolve with stopping the aluminum or by chelation. Data in children have been sparse and more difficult to define clearly in that other major variables, including malnutrition, contribute to poor growth and development. In this review, evidence for aluminum toxicity in children will be emphasized.

Historical survey

The historical survey of aluminum-related diseases documents the chronological order of the published data concerning aluminum toxicity [1].

1928	Smith reports that feeding aluminum-containing baking powder to dogs causes an increase in organ aluminum [2].
1950–1960	Aluminum is advocated as a phosphate binder in renal failure [3].
1962	Encephalopathy is noted in a factory worker who inhaled aluminum [4].
1969	Disabling fracturing osteomalacia is reported in hemodialysis patients in Newcastle [5].
1970	Berlyne et al. [6] demonstrate elevated aluminum levels in patients with renal failure.
1972	Alfrey et al. [7] document encephalopathy in dialysis patients.
1976	Alfrey et al. [8] report encephalopathy associated with high aluminum levels.
1977	Baluarte et al. [9] report on encephalopathy in children with renal failure.
1978	Ward et al. [10] report on osteomalacia related to aluminum toxicity.
1980	Ackrill et al. [11] report reversal of encephalopathy after chelation of aluminum.
1980	Short et al. [12] associate aluminum toxicity with microcytic anemia.
1983–1984	Andreoli et al. [13], Griswold et al. [14], and Sedman et al. [15] separately report on hyperaluminemia associated with encephalopathy and metabolic bone disease in children receiving aluminum-containing antacids. Serum and tissue levels are correlated with the oral dose of aluminum.
1984	Salusky et al. [16] document the role of aluminum hydroxide in raising aluminum levels in children on continuous ambulatory peritoneal dialysis (CAPD) again correlating aluminum levels with oral intake.
1985	Andreoli et al. [17] improvement in a child with aluminum toxicity after treatment with deferoxamine.
1985	Sedman et al. [18] report aluminum loading in premature infants who receive contaminated i. v. fluid.

1985 Slanina et al. [19] report increased aluminum absorption in combination with citrate.

1986 Slatopolsky et al. [20] document calcium carbonate ($CaCO_3$) to be a good substitute for aluminum compounds as a phosphate binder.

1986 Salusky et al. [21] document the successful use of $CaCO_3$ as a phosphate binder for children.

1989 Sedman et al. [22] report no evidence of aluminum toxicity in children with kidney failure if pharmacological doses of aluminum or contaminated parenteral solutions are avoided.

1990 The Food and Drug Administration (FDA) recommends to all makers of parenteral solutions that concentrations of aluminum should not exceed 25 μg/l [23].

1990 Salusky et al. [24] show no aluminum accumulation in infants on continuous cycling peritoneal dialysis (CCPD) who have not received aluminum-containing antacids or parenteral nutrition.

1991 Tsou et al. [25] document that normal infants who receive aluminum-containing antacids have elevated serum levels of aluminum.

1991 Salusky et al. [26] show that aluminum accumulates in individuals on "low-dose" therapy of aluminum-containing antacids and show $CaCO_3$ to be superior to aluminum-containing antacids for phosphate binding in children with renal failure.

Chemistry of aluminum

Although aluminum comprises approximately 8% of the earth's crust and is ubiquitous in nature, it is found only in small amounts in normal mammals. Due to its small radius and high oxidation potential, aluminum most commonly exists in combined forms of aluminosilicates such as clays, micas, and feldspars. Impure oxides make up bauxite, the primary ore which is found in weathered terrain. Alums and other related aluminum sulfates have often been added to drinking water to decrease turbidity. Aluminum is amphoteric and, in aqueous solution, forms many different species depending on the pH of the solution. Only small amounts of free aluminum exist at pH 6.5–7.4. As the pH moves above and below this range, more free aluminum is available; thus, acid rain is felt to be causal in releasing aluminum from its bound form and hence causing toxicity to fish [27]. Aluminum compounds are usually poorly absorbed by the gastrointestinal tract, but citrate complexes of aluminum increase aluminum absorption. The citrate-aluminum complex has a zero charge that allows it to pass through membranes, while aluminum phosphate and aluminum hydroxide are relatively insoluble. Slanina et al. [28] have demonstrated conclusively that aluminum blood levels of humans taking aluminum-containing antacids rise substantially with the addition of citrate.

Transferrin is felt to be the leading plasma protein that binds aluminum. Albumin and globulin proteins of plasma bind metal ions such as aluminum weakly. The cerebrospinal fluid lacks significant amounts of transferrin, and aluminum sequestered in the central nervous system (CNS) could potentially be more toxic than aluminum in the serum. Aluminum could potentially interact with kinases, polymerases, and regulatory proteins. Aluminum can most easily substitute for magnesium in biological systems and could inhibit any magnesium-dependent reactions [29].

Absorption of aluminum

The skin and gastrointestinal and respiratory tracts are substantial barriers to aluminum. However, the fraction of aluminum that is absorbed becomes important if the volume taken in is large, the absorbed fraction is increased, or aluminum excretion is impaired as is the case in renal failure. There are no radioactive aluminum isotopes suitable for metabolic studies. Since aluminum levels in living systems are extremely low and measurement of aluminum is fraught with difficulty secondary to matrix interference, accurate metabolic balance studies have been difficult. The available data in adults are from Greger and Baier [30]. Kaehny et al. [31], and Alfrey [32]. Greger and Baier [30] did 40-day balance studies in adult males at two levels of aluminum intake. More than 96% of aluminum ingested was recovered in feces, and the rest was recovered in urine. No long-term retention of aluminum was detected. The study of Kaehny et al. [31] of short-term loading with

Table 1. Estimate of aluminum (Al) absorbed from various sources

At risk group	Al intake	Al absorbed	Estimated retention
Normal adults 70 kg	3–5 mg/day	0.04–0.07 μg/kg per day	0%
Individual ingesting 30 ml Al-containing antacid	3,600 mg/day		
70-kg adult		42 μg/kg per day	Documented only in
10-kg child		360 μg/kg per day	renal insufficiency
Newborn ingesting cow's milk formula 4-kg infant	160–320 μg/day	0.08 μg/kg per day	Unknown
Infants receiving i. v. therapy 0.75-kg infant	10–20 μg/day	15–30 μg/kg per day	78%

aluminum-containing antacids in adults showed between 0.1% and 0.5% absorption with subsequent excretion in the urine. Alfrey's studies [32] of autopsy specimens showed exceedingly low levels of aluminum in the tissues of individuals with normal renal function who died of nonrenal-related diseases. The data support the idea that adults with normal renal function absorb between 0.1% and 1% of oral aluminum intake and retain nondetectable amounts of aluminium. The data from children are scant but, again, show that children who die with normal renal function and only the usual environmental exposure have only small amounts of aluminum in their tissues [22]. Nevertheless, it has been clearly documented that children who receive large quantities of aluminum as a contaminant of parenteral nutrition solutions and who have no fecal excretion, can retain as much as 78% [18].

If we extrapolate from the intake of the adults and look at the normal exposure of children through food and formula, we can make some general comparisons. As can be seen in Table 1, a normal adult will ingest 3–5 mg/day aluminum with the usual exposure to foodstuffs and the environment. Assuming a 0.1% intestinal absorption of aluminum, a 70-kg adult will absorb only 0.04–0.07 μg/kg per day. Newborns ingesting cow's milk formula will absorb no more aluminum than normal adults, but infants receiving parenteral nutrition or other forms of i.v. therapy, or adults with impaired renal function ingesting antacids are at risk of retaining aluminum in the tissues with the potential for adverse consequences.

Metabolism of aluminum

The absorbed fraction of aluminum is bound rapidly to the tissues – the remaining free aluminum is excreted through the kidneys – however, aluminum clearance is about 5% of glomerular filtration rate secondary to protein binding [33]. There is also excretion in bile and evidence of increased aluminum deposition in bone in patients who have liver disease, implying that this route of excretion can become important in some circumstances; although, in general, it represents a very small amount [33].

Aluminum can also enter the body through respiratory exposure and has been documented in workers exposed to aluminum dust. Most aluminum dust will simply accumulate in the lungs. Industrial workers chronically exposed to inhaled aluminums do have higher blood and urine aluminum levels. Encephalopathy from inhalants has been reported [34, 35].

Measurement of aluminum

Accurate and precise methods of analysis of metals involved in biological systems are crucial for clinical studies. Although there were inferences of aluminum toxicity prior to the 1970s, conclusive data relating aluminum toxicity to encephalopathy awaited a method of analysis that could accurately distinguish aluminum levels in normal healthy individuals from those in individuals with toxicity. Since normal individuals have serum levels of aluminum <20 μg/l and toxicity was documented at 100 μg/l, the analytical method must be accurate and reproducible in the parts-per-billion range.

Although this could be achieved in simple aqueous solutions by several methods, measuring aluminum in serum and tissues required overcoming matrix interference. This can be done most accurately and economically by flameless atomic absorption, which is considered the method of choice today [36]. The methodology is still difficult and operator dependent; each laboratory must use internal as well as external standards supplied by the National Bureau of Standards (reference material no. 8419). Sample contamination is an ongoing issue since aluminum-containing dust is virtually everywhere. Deodorants and body powders contain aluminum, making balance and autopsy studies complicated. Samples collected for aluminum determination must be handled with careful cleansing of the skin and stored in trace-element-free containers. Measurement of tissue aluminum has been performed successfully by a small number of laboratories, and methods vary [36]. Preparation of tissue can markedly change the aluminum determination, and interlaboratory variation may be significant.

A crucial question has been whether serum aluminum levels reflect tissue loading. In both animal and human studies, the answer is no. Since aluminum is highly protein bound, tissues may become loaded while serum levels remain relatively low, especially during chronic loading. The only prospective data in infants come from Bozynski et al. [37] who studied twin preterm infants who died and whose tissues were available for analysis. Despite only moderately elevated serum aluminum levels (25–50 μg/l, mean of 12 samples during life), one twin had 2–6 times the amount of aluminum in his tissues compared with the other. Both sets of tissues indicated significant aluminum loading.

Sources of aluminum

Background exposure to aluminum is constant but seems to have relatively little consequence as the total aluminum load of normal humans is usually <30 mg [36]. Many plants sequester aluminum. Consequently, foods can contain significant amounts of aluminum. Normal intake in the western society would usually be 3–5 mg aluminum consumed/day. Ground water contains between 10 and 15 μg/l but this can rise to as high as 1,000 μg/l if contaminated by volcanic ash. Aluminum sulfate is also added to water in many water treatment plants to decrease the turbidity and was the primary cause of dialysis units having epidemics of encephalopathy in areas where tap water so treated was used for dialysate.

Consumers have long been concerned about aluminum utensils even though the amount of aluminum leeched into foods is infinitely small compared with that ingested in the form of aluminum-containing antacids. One would have to consume 18 kg rhubarb that had been boiled in an aluminum pot in order to ingest the amount of aluminum contained in one tablespoon of aluminum hydroxide suspension such as Amphojel (Wyeth-Ayerst Laboratories,

Table 2. Representative values of Al content in i. v. solutions[a, b]

	Al/ μg per l
Potassium phosphate	16,598
Sodium phosphate	5,977
Calcium gluconate	5,056
25% Albumin	1,822
5% Dextrose	72
TPN – high calcium and phosphate	306
Ringer's lactate	35

TPN, Total parenteral nutrition
[a] Adapted from references 1 and 18
[b] Measurements will vary from batch to batch

Table 3. Representative values of Al content in oral substances[a, b]

	Al
Amphogel[c]	636 mg/30 ml
Alternagel[d]	966 mg/30 ml
Maalox[e]	360 mg/30 ml
Sucralfate[f]	207 mg/1,000 mg tablet
Kaopectate[g]	100 mg/100 ml
Seawater	0.001 mg/1,000 ml
Tap water (Colorado)	0.012 mg/1,000 ml
Breast milk (Colorado) ($n = 12$)	0.009 ± 0.006 mg/1,000 ml
Cow's milk based formula	0.266 mg/1,000 ml
Soy formula	1.4 mg/1,000 ml
Spinach	87 mg/100 g
Rhubarb boiled in Al foil	1.62 mg/100 g

[a] Adapted from references 1 and 18
[b] Measurements will vary from batch to batch
[c] Wyeth-Ayerst Laboratories, Pa., USA
[d] Johnson and Johnson, Merck, Pa., USA
[e] Rhone-Poulenc, Pa., USA
[f] Merion-Merrell Dow, Mo., USA
[g] Upjohn, Mich., USA

Pa., USA). Tables 2 and 3 list aluminum levels of commonly used substances. Infant formulas contain small amounts of aluminum secondary to contamination of calcium and phosphate salts that are added. Formulas which require an addition of more calcium such as soy formulas will have higher levels. In these cases, the amount of aluminum is small and would be close to that which a child begins to ingest when he or she eats table food.

Aluminum-containing antacids and medication such as sucralfate (Carafate Merion-Merrell Dow, Mo., USA) and attapulgite (Kaopectate Upjohn, Mich., USA) are made up of aluminum compounds. The important point is that aluminum-containing antacids contain approximately 10^5 more aluminum than any foodstuff that can be eaten. Aluminum hydroxide suspension contains 32,167,800 μg/l versus formula which contains 250 μg/l aluminum.

Parenteral solutions can be contaminated with aluminum on the basis of salts being added to the solution. Casein was also highly contaminated with aluminum. The Food and Drug Administration has now recommended a level of no more than 25 μg/l in all parenteral solutions [23]. However, compliance at this point is voluntary, and there can be a wide variation in aluminum levels in similar solutions [18]. Highly contaminated dialysate made from tap water was the original cause of severe aluminum toxicity but this has been eliminated by stringent control of the quality of water used for dialysate. Intermittent cases of severe toxicity have occurred when previously safe water has been suddenly altered. This happened in the State of Washington after Mt. Saint Helens erupted and when groundwater supplies which previously had contained 2–10 μgl aluminum changed to 125 μg/l. Contaminated dialysate is extremely dangerous since the aluminum is highly protein bound in the body which creates an "infinite sink" to dialysate aluminum passing by the blood stream in large volumes.

Evidence of aluminum toxicity in childhood

Since Alfrey et al. [8] linked elevated aluminum levels in tissues to encephalopathy in adult dialysis patients in 1976, a plethora of data has accumulated correlating increased aluminum in tissues with encephalopathy, metabolic bone disease, and microcytic anemia in adults. There was little recognition of toxicity in children until 1977, when Baluarte et al. [9] reported five children with a progressive encephalopathy that was similar to dialysis dementia. These children had never been treated with dialysis but had received aluminum-containing antacids. At the time of the report, the aluminum levels were not available. In 1980, the worldwide pediatric occurrence of aluminum encephalopathy was established by surveying 96 pediatric nephrology programs. Fourteen centers reported 24 affected children, none of whom had been on dialysis but all of whom had received aluminum-containing antacids [38]. In Denver, we saw five affected children who were receiving both citrate and aluminum-containing antacids between 1981 and 1983.

Subsequently in 1983 and 1984, reports from Andreoli et al. [13] Griswold et al. [14], and Sedman et al. [15], specifically linked high aluminum levels in tissues and blood to disease in 18 children. The amount of oral aluminum ingested was directly related to serum levels. In a retrospective review, the children who had received citrate seemed most severely affected. Children with serum levels >100 μg/l (normal <10 μg/l) showed developmental delay and abnormal bone formation. Bone, blood, and CNS manifestations will be examined separately in later sections of this paper. The majority of the severely affected children were infants with dysplastic kidneys who had relatively high urine outputs. Acidosis prompted the use of citrate, and the children often were given high-dose, aluminum-containing antacids to control hyperphosphatemia. Subsequently, seizures and severe developmental delay ensued. A child reported from our practice with dysplastic kidneys and renal insufficiency at birth had normal developmental testing prior to the age of 2 years [39]. After 4 years of aluminum-containing antacids, she had personality changes and loss of communication skills. She then developed poorly controlled seizures. [Aluminum levels were 220 μg/l in serum (normal <10 μg/l) and bone aluminum was 165 mg/kg (normal <3.3 mg/kg)]. Developmental testing at that point showed her to be severely delayed. At the time of that testing, her blood urea

nitrogen was 30 mg/dl, all other metabolic parameters were stable, ruling out uremia as contributory. Despite therapy with deferoxamine, she subsequently died. Brain aluminum was found to be elevated at 45 mg/kg dry weight gray matter (normal = 2.18 ± 0.69). This level was compatible with the level seen in encephalopathic patients in the original adult study of Alfrey et al. [8] – the mean of adult patients with encephalopathy was 24.98 ± 9.10 mg/kg.

A patient described by Andreoli et al. [17] had hemolytic uremic syndrome at age 13 months. Over the next 6 years, he was given aluminum hydroxide. At 5 years, he displayed severe bone pain, myopathy, microcytic anemia, and failure at school. At 6 years, he developed poorly controlled seizures. Serum aluminum was 252 μg/l (normal <10 μg/l). A bone biopsy showed generalized osteomalacia and positive aluminum staining (no quantitation was done). Aluminum hydroxide was stopped and intraperitoneal deferoxamine therapy was started. The child improved dramatically but did not return to normal. When chelation was stopped because of an intercurrent illness, his seizures worsened. The child subsequently died of infectious complications.

A recent report by Moreno et al. [40] describes acute aluminum toxicity secondary to bladder irrigations with aluminum sulfate in a 4-year-old boy with rhabdomyosarcoma who had developed renal failure and hemorrhagic cystitis after ifosfamide. His serum aluminum level was documented at 135 μg/l (normal <10 μg/l) at the time he became encephalopathic and developed seizures. The calculated dose of aluminum sulfate from the bladder irrigation was 1.89 g elemental aluminum. (Normal daily exposure is 3–5 mg/day). The aluminum sulfate was stopped and within days his neurological status returned to normal. It took 45 days for the aluminum levels in serum to return to normal, implying that his tissues had been loaded. The child recovered without any form of chelation [40]. An important point about this child is that the acute aluminum toxicity presented as obtundation and seizures rather than dementia.

Salusky et al. [26, 41] have produced an important body of literature on the incidence of metabolic bone disease in children who receive aluminum-containing antacids. In 1988 Salusky et al. [41] reported bone histology in 44 pediatric patients undergoing CAPD or CCPD at a time when aluminum had begun to be limited. Only children who received aluminum-containing antacids had osteomalacia – children with stainable aluminum on bone histology had a mineralization lag time of 975 ± 1,422 days versus 26 ± 30 days (P <0.05). Plasma aluminum levels correlated directly with intake of aluminum-containing antacids. In 1991 Salusky et al. [26] reported on the bone histology of 17 children, 7 of whom were receiving aluminum hydroxide at 30 mg/kg per day maximal dose compared with 10 children receiving only $CaCO_3$ as phosphate binder. They showed that even on low-dose aluminum hydroxide there were elevated serum aluminum levels and histologically proven aluminum deposition in bone. The most important information in this study is that children whose hyperphosphatemia was controlled by $CaCO_3$ had much better control of serum phosphorus levels, higher serum calcium levels, and a more favorable histological response to calcitriol. Children on even low-dose aluminum hydroxide had a high rate of progression of secondary hyperparathyroidism.

Premature infants with limited renal function may also be at risk of aluminum-related disease. Reports from Sedman et al. [18] and Koo et al. [42] documented that these infants have high levels of tissue aluminum. Eighteen premature infants admitted to an intensive care unit were studied by Sedman et al. [18]. They had been treated by i.v. therapy and were compared with 8 term infants who were not given i.v. therapy. Thirteen of the premature infants who received i.v. fluids had a second plasma aluminum measurement after an interval of 3 weeks while receiving formula. Plasma aluminum concentrations for infants receiving i.v. fluids were significantly higher than for those infants on only oral feedings [36.7 ± 45.3 μg/l versus 5.17 ± 3.1 μg/l (mean ± SD) P <0.0001]. The report also showed data for 5 infants who had 2- to 3-day urinary balance studies while on parenteral nutrition with negligible stool losses. The infants' daily urinary excretion of aluminum was approximately 20% of that administered i.v.. Data on bone aluminum concentration from autopsy specimens collected from 23 infants demonstrated that the bone aluminum concentration was 10 times higher in the 6 infants who had received at least 3 weeks i.v. fluid therapy than in the 17 infants who had never received i.v. therapy. Koo et al. [42] studied 20 infants with gestational ages of 29–41 weeks with the mean duration of parenteral nutrition as 43 days. The data were similar to those reported by Sedman et al. [18] and demonstrated that parenteral solutions were contaminated with aluminum, renal elimination of aluminum was incomplete, and bone deposition of aluminum occurred. Vileisis et al. [43] also confirmed a high concentration of aluminum in parenteral solutions and in the urine of premature infants, raising the issue as to whether or not aluminum is a factor causing bone disease in these infants. However, bone histology in premature infants is difficult to standardize. Since there are multiple other variables causing problems in these infants, no absolute evidence of aluminum-induced bone toxicity can be cited. It can only be noted that tissue levels are higher than in control infants.

The above examples cite evidence that children who received either pharmacological oral doses of aluminum or parenteral solutions contaminated with aluminum had tissue loading. No one has clearly shown toxicity from doses of aluminum that are considered to be in the background range (i.e., that of normal food intake and environmental exposure).

Of concern in the recent past was a report by Freundlich et al. [44] which described two infants who appeared to develop aluminum toxicity with encephalopathy from formula intake. They had no known parenteral or oral aluminum from antacids. These infants died and subsequently had analysis of brain aluminum. The paper stated that one infant died after 30 days of life having taken only approximately 150 ml formula/day. Brain aluminum was measured at 47.4 μg/g tissue (normal <0.1 μg/g). Calculations from data in the paper showed that over 30 days a total of approximately 1,125 μg could have been ingested from formula. If we calculate even 10% absorption (in

reality the figure should be <1%), then the child's brain could have been exposed to a total of 112.5 μg. If we assume a 100-g brain, then the total brain aluminum would be extrapolated to 4,140 μg – at least 40 times what is reasonably possible by the ingestion history. The difficulties with the study are many. No controls were reported, resulting in a lack of knowledge of a mean and SD of brain aluminum levels in the age group studied by the laboratory doing the analyses. The method used by the authors to analyze the infant brain included nitric acid digestion, which has been documented by Alfrey [36] to produce unreliable results thought to be secondary to nitrogen residues in the graphite tube which affects the aluminum signal. These data have not been reproducible.

Subsequent papers showed no evidence of aluminum loading in children with formula intake only. Salusky et al. [24] followed 16 infants receiving milk formula PM 60/40 (Ross Laboratories, Ohio, USA) and measured both serum and bone aluminum levels. No child had elevated levels. Combined data from our program and the Growth Failure in Renal Disease trials measured serum aluminum in 76 individuals and tissue aluminum in 16 children [22]. Elevated aluminum levels were only found in children exposed to aluminum-containing antacids or prolonged parenteral nutrition. One child had been born prematurely with severely dysplastic kidneys at 32 weeks' gestation. She was dialyzed and supported with PM 60/40 for a number of months, then had a successful renal transplant. She appeared developmentally normal. She subsequently died of cytomegalovirus infection. The brain was analyzed for aluminum, showing 1.56 mg/kg dry weight (normal in adults 2.18 ± 0.69 mg/kg dry weight). Therefore, we have no further evidence that the aluminum content of food or formula in the levels so far documented causes aluminum toxicity.

A recent paper from Tsou et al. [25] measured serum aluminum in ten infants with normal renal function who had received aluminum-containing antacids for at least 1 week for gastric complaints, such as gastric reflux or presumed dyspepsia. The study patients consumed 123 ± 16 mg/kg per day elemental aluminum. Their plasma aluminum level was 37.2 ± 7.13 μg/l, significantly elevated compared with control levels of 4.13 ± 0.66 μg/l ($P < 0.005$). These levels correspond to levels that have previously been shown to be associated with aluminum loading of tissues [37].

In summary, numerous clinical data from pediatric programs have documented an encephalopathic syndrome and abnormal bone histology in children who are given aluminum-containing antacids. Salusky et al. [26] demonstrated abnormal bone histology in children who received as little as 30 mg/kg per day for a year. Withdrawal of aluminum or chelation has resulted in significant clinical improvement. Both the Food and Drug Administration and American Academy of Pediatrics have recognized that aluminum toxicity exists and recommended limiting patient exposure [23, 45].

Pathophysiology and clinical syndromes of metabolic bone disease, anemia, and CNS toxicity

The data presented so far concerning aluminum toxicity have been from observational epidemiological studies. Elucidating the specific effects of aluminum requires use of animal models or in vitro models to control the confounding variables such as uremia. However, there are still confusing factors. Aluminum is thought to decrease gastric motility and appetite, and animals that chronically receive aluminum may become malnourished. Pregnant animals that are exposed to aluminum may not eat adequately to support fetuses with the result that studies that report CNS toxicity in fetuses may really be reporting nutritional abnormality instead of direct fetal toxic effects. With these limitations in mind, we will briefly review the literature on how aluminum causes toxicity, specifically in bone, CNS, and red blood cells. We will define the classic clinical syndromes that have been described in pediatric patients.

Metabolic bone disease

In normal bone, there is a continuous process of resorption and formation termed remodeling. Remodeling is tightly regulated at tissue and cellular levels to maintain mineral balance in the mature skeleton and to allow growth in the juvenile skeleton. This process can be evaluated by utilizing dynamic bone histology, i.e., by labeling bone with tetracycline and quantitatively measuring the bone mineralization that occurs between the two labels.

Pathophysiology. When aluminum is given to animals by parenteral routes, a number of processes are observed by quantitative histology. The animals develop a de novo osteomalacia or lack of mineralization. Ellis et al. [46] noted that growing rats developed a band of poorly mineralized bone just below the growth plane in the proximal tibia which failed to calcify even after injections of aluminum were stopped, showing effects were sustained for several weeks.

A number of different mechanisms have been proposed for this inhibition of mineralization. Direct effects could include reduction of bone crystal seeding, altered crystal growth, impaired mineral entrance, or disturbances of collagen maturation or linkage. Indirect effects could include altered metabolism of vitamin D, resistance to the actions of vitamin D, or altered osteoblast metabolism [47]. In order to sort out these mechanisms, rapidly growing, 8-week-old, pair-fed piglets were given i.v. injections of aluminum. They had no renal failure. The piglets developed profound osteomalacia, and bone formation rate was markedly reduced primarily because of reductions in the active sites of formation [48]. It seemed as if the aluminum was inhibiting the proliferation of osteoblasts. A study by Talwar et al. [49] of in situ bone formation in demineralized bone matrix was consistent with the theory of osteoblast inhibition.

There is ongoing debate as to the direct effect of aluminum on parathyroid hormone (PTH) secretion, which could alter bone formation rate. The weight of the evidence

would support aluminum causing increased resistance to PTH. Hypercalcemia, which accompanies aluminum bone disease, may also suppress PTH release [50].

Clinical syndrome. Regular hemodialysis was begun in Newcastle in November 1963. In 1965, the Newcastle renal unit reported a syndrome of painful feet with severe demineralization of bone noted on X-ray [5]. This was distinctly different from previous reports of hyperparathyroid bone disease often seen in chronic renal failure. Subsequent papers described severe osteomalacia on bone biopsy, low serum alkaline phosphatase, intermittent hypercalcemia, and poor responsiveness to vitamin D. Eventually, the patients experienced multiple fractures that healed poorly and eventually the disease was termed "fracturing osteomalacia" [10]. Epidemics seemed to occur in specific areas, and certain centers had a high prevalence and others a low prevalence of fracturing osteomalacia. Once aluminum-related encephalopathy was described in 1976, it was found to correlate closely with fracturing osteomalacia, indicating that aluminum was the etiological agent. Full water treatment, with reverse osmosis and deionization which removes aluminum, was installed by the late 1970s, and the aggressive bone disease disappeared in most units, although subclinical bone disease was sustained secondary to use of aluminum-containing antacids.

Andreoli et al. [13] published the first quantitative histological reports in three children with renal insufficiency, but not on dialysis, who received aluminum-containing antacids and demonstrated severe osteomalacia and massive deposition of aluminum in bone. Subsequent studies by Salusky et al. [16, 21, 26, 41] further elucidated the syndrome. In general, these severely affected infants had poor growth, muscle weakness, and osteopenia on X-ray. Standard radiographs also demonstrated fraying of metaphyses of long bones and widening of the physis [51]. Withdrawal of aluminum and subsequent chelation resulted in return of calcification, but in an unusual pattern with calcification of the long bones beginning at the most recently formed osteoid and proceeding toward the diaphysis. This healing pattern created lucent defects and transient bone-within-bone appearance. Recently Salusky et al. [26] found aluminum-related bone disease (osteomalacia) in a patient who only received aluminum hydroxide for 1 year with a moderate dose of $\leq$30 mg/kg per day elemental aluminum.

In summary, metabolic bone disease is readily created in animal models by exposure to aluminum, including those without renal disease. Epidemiological studies in dialysis units related aluminum-contaminated dialysis to severe fracturing osteomalacia which resolved when water was treated adequately. Quantitative bone histology in children has demonstrated osteomalacia in children associated with aluminum deposition in bone which resolves with removal of aluminum.

Anemia

The usual anemia of chronic renal failure is normocytic and normochromic and is directly related to deficiency of erythropoietin. The causal relationship between anemia and aluminum intoxication was reported by Elliot et al. [52] in 1978. Retrospectively, it was noted that a decrease in hemoglobin often preceded the onset of encephalopathy in individuals with aluminum toxicity.

Pathophysiology. The precise mechanism leading to microcytic anemia from aluminum exposure is unknown but is postulated to be similar to that lead from exposure. Aluminum may inhibit δ-aminolevulinic acid synthetase [53]. In addition, since aluminum is bound to at least one of the specific iron sites of transferrin, it may also alter iron metabolism.

Clinical syndrome. Clinical features of aluminum-induced anemia include decreased mean corpuscular volume (MCV) and decreased mean corpuscular hemoglobin concentration with hypoproliferative marrow. Serum ferritin and iron levels are normal. Reversal of aluminum-induced anemia is usually complete when aluminum administration is stopped [53].

Andreoli et al. [13] documented microcytic anemia in three children with high aluminum levels. These children had encephalopathy and severe bone disease. Shah et al. [54] meticulously documented the progression of a child's hematological status prior to receiving aluminum when the MCV was 77 fl, during aluminum administration when the MCV reached 55 fl, and then during recovery from aluminum toxicity when the MCV returned to 79 fl. Prior to the recognition of high aluminum levels, extensive studies in this patient were done to rule out other causes of microcytosis. Iron studies had shown normal ferritin, normal serum iron, normal total iron-binding capacity, and normal iron stores in the marrow. The child was unresponsive to iron therapy. Thalassemic syndromes were ruled out by normal hemoglobin A_2 and F and by documentation of normal MCV early in life (MCV was 108 fl as a newborn). Other causes were excluded by normal pyridoxine levels, lack of sideroblasts in the marrow, and absence of chronic inflammation. The patient's MCV of 55 fl coincided with an aluminum dose of 268 mg/kg per day. Elevated serum aluminum levels were documented several months after discontinuation of the oral aluminum, when the serum level was 80 μg/l and the bone was measured at 260 mg/kg (normal 3.3 mg/kg dry weight). At the beginning of aluminum therapy, the child's developmental level was normal with speech and normal walking. During the highest aluminum dosage, she became profoundly delayed and was unable to walk. Months after cessation of aluminum, developmental milestones were reported to improve markedly. No chelation was performed.

In summary, aluminum toxicity is associated with microcytic anemia. Although the anemia may precede encephalopathy, its occurrence in children has only been reported with other profound effects of toxicity.

CNS toxicity

Pathophysiology. The complexity of the CNS makes isolating the effects of aluminum difficult. Aluminum is

thought to affect at least 70 different transport and enzyme systems in the CNS [55]. These effects may vary widely depending on the species of animals tested, the dose of aluminum given, and the method of administration. Since aluminum is highly protein bound to transferrin and transferrin may be unavailable in the cerebrospinal fluid, aluminum will equilibrate in the CNS to higher free levels compared with serum, and is more available to interfere at metal binding sites. Data would suggest that aluminum can inhibit systems involved in the uptake of choline, glutamate, γ-aminobutyric acid, and serotonin. Crapper et al. [55] postulate that aluminum replaces magnesium at a key DNA-protein binding site. Because the aluminum atom has a small ionic radius and a high charge, it is nearly one million times slower than the magnesium atom in dissociating from the DNA-protein complex. By replacing magnesium, aluminum could effectively lock repressor proteins causing dysregulation of protein synthesis in the brain.

Sensitive species, such as cats and rabbits, demonstrate highly reproducible signs of memory and learning impairment with a single intracranial administration of soluble aluminum salts which raises their aluminum content in gray matter fourfold from 1.5 mg/kg dry weight to 5.5 mg/kg dry weight. (In the original study of Alfrey et al. [8] of dialysis dementia, patients' brain gray matter levels of aluminum were 24.98 mg/kg dry weight.) Seven to ten days after injection, cats exhibited progressive impairment of motor control during jumping and alterations in performance of learning and memory tasks. Shortly after memory defects appeared, cats and rabbits exhibited progressive deterioration in motor control, ataxia, tremors, myoclonic jerks, and seizures. Aluminum-toxic animals may survive but have persistent severe neurological and behavioral defects [56–58].

Clinical syndrome. Only those who cared for children in the late 1970s during liberal use of aluminum-containing antacids and citrate can appreciate the horror of helplessly watching previously normal children die of severe encephalopathy over months to years. Foley et al. [59] provided an excellent description of five such children. These children were most often those with renal dysplasia who, after being placed on aluminum, developed mild ataxia, dysmetria, tremors, and hyperreflexia. At the second stage, their ataxia became marked, and the children lost the ability to walk. There was regression of cognitive and motor function and saccadic ocular movements. In stage three, the children lacked response to auditory and visual stimuli and had absence following reflexes. There were no volitional movements. Death usually ensued. Dialysis and/or transplant in stage three rarely led to recovery. Variations of encephalopathy depended on the type of aluminum dosing and degree of renal failure. A patient of ours [39] had relatively good renal clearance and her encephalopathy progressed over 5–6 years. She never became comatose although she eventually died with massive gastrointestinal bleeding and intractable seizures. We have seen other children with chronic seizures and severe developmental delay associated with chronic exposure to aluminum. However, infants with renal failure can have significant developmental problems without aluminum exposure. Rotundo et al. [60] reported that 20 of 23 children with renal failure from their program had significant developmental delay and/or seizures. He reported no coincidental aluminum exposure in 4 of these children, but aluminum levels were not measured and the patients tended to come from a referral population where long-term medical records were not available.

The post-high-dose-aluminum era (since 1984 in most pediatric nephrology programs) has shown complete eradication of the profound encephalopathy syndrome. Infants who are anephric on dialysis still show significant motor delays but rarely have severe regression of cognitive function or intractable seizures. Children with successful renal transplants do remarkably well even after several years of dialysis as infants [61]. Two patients in our program have been anephric on dialysis since infancy, with a total dialysis experience of approximately 7 years each. Both children have had several rejected transplants and now high antibody status. With aggressive dialysis and nutritional support, they have grown within normal percentiles, function well in age-appropriate grades, and have a decent quality of life despite the inherent difficulties of chronic dialysis. These patients provide some reassurance that other processes involved in long-term dialysis care are not as neurotoxic as the combination of citrate and aluminum. In 1989 Geary and Haka-Ikse [62] stated "the development of children with chronic renal disease has improved markedly . . . it may have resulted from a shift in emphasis in renal failure management at the hospital. The use of aluminum-containing antacids has been virtually eliminated. A more aggressive approach to ensure optimal nutrition has been adopted . . ."

In summary, the use of aluminum-containing antacids in combination with citrate produced encephalopathy that was documented in many centers. We no longer see this syndrome. Many other factors in the care of children with renal failure have changed in the last decade, most prominently nutritional support. These factors have also changed the long-term neurological prognosis of children with renal failure [62].

Diagnosis

Aluminum toxicity should be suspected in individuals who have had pharmacological exposure to oral aluminum or contaminated parenteral fluid. Since man evolved in an environment where normal intake was approximately 3–5 mg aluminum/day, we can assume that this type of exposure is safe. Since normal absorption of this amount would be 1% or less, then a safe parenteral exposure could be extrapolated to 30 μg or less/day. However, this is all conjecture. As is the case in lead toxicity, no safe exposure is easily defined since aluminum has no known physiological role in mammals.

Absolute diagnosis of toxicity can only be made by analysis of tissue. Since chronic, low-dose exposure to aluminum can cause significant loading in tissue without concurrently high levels in serum [37], monitoring serum levels could be reassuring if <10 μg/l but, otherwise, cannot be conclusive as far as ruling out tissue loading.

Deferoxamine testing has been utilized in the adult population for diagnosing tissue loading, but is not without complications and has been relatively unhelpful in pediatrics [26]. Any individual with a serum level of aluminum by flameless atomic absorption of >100 μg/l, who has encephalopathy, should be assumed to be aluminum toxic. Children with failure to thrive and osteopenia, who have been exposed to aluminum, should have a bone biopsy followed by quantitative histology and aluminum staining.

Children on prolonged parenteral nutrition, who receive large doses of albumin, or who are given chronic oral doses of aluminum-containing substances, should be monitored. If serum levels begin to rise to >20 μg/l, all sources of aluminum should be stopped. Since aluminum toxicity is iatrogenically caused, diagnostic dilemmas would cease to exist if aluminum exposure could be avoided.

Prevention and therapy

The major method of preventing aluminum toxicity is to avoid pharmacological doses. The American Academy of Pediatrics and the Food and Drug Administration recommend decreased exposure to aluminum from antacids and parenterally administered solutions [23, 45]. Unexpected aluminum toxicity from bladder irrigations [40] and previous poorly recognized aluminum-containing medications (Kaopectate) can be treated simply by stopping the aluminum. At the November 1991 American Society of Nephrology meeting, Dr. Jack Coburn stated that the severe complications of deferoxamine therapy including death from infections such as *Yersinia* and *Rhizopus* can cause fatality in approximately 30% of patients, and, therefore, the first line of therapy for aluminum toxicity should always be to stop all the known aluminum exposure, even though aluminum is occasionally unavoidable as a contaminant. Citrate complexed with aluminum is so much more easily absorbed than other forms of aluminum that perhaps citrate use should be limited in renal failure patients. However, since no documentation of true toxicity has taken place outside the published observations already cited, we would hesitate to say that this is absolutely necessary.

Phosphate in the diet should be aggressively limited to avoid hyperphosphatemia. This demands a level of compliance that most patients find difficult. In North America, the average phosphorus intake ranges from 140 to 2,000 mg/day. It should be recalled that cow's milk contains 1,200 mg phosphorus/l so children who ingest large amounts of dairy products quickly exceed the suggested limits of 10–15 mg/kg per day. Fifty to eighty percent of ingested phosphorus is absorbed. Phosphate removal is limited in dialysis because it is an ionized molecule. Our approach in infants is to use the lowest phosphate formula available that fulfills the other needs of that particular infant. Formulas such as PM 60/40 and S29 (Wyeth-Ayerst Laboratories, Pa., USA) are very helpful. Most patients require extra sodium supplementation. Older children are liberalized to a regular diet but not allowed to drink cow's milk. A low-phosphate milk substitute such as Alterna (Ross Laboratories, Ohio, USA) may be used instead. When a child comes to clinic with poorly controlled hyperphosphatemia, we may limit all normal food intake for several days and use one of the nutritional supplements that is limited in phosphorus such as Replena or Nephro (Ross Laboratories, Ohio, USA) which will give complete nutrition with low phosphate intake.

If the child is aluminum toxic and has CNS and bone disease, then deferoxamine may be indicated [63]. In children on peritoneal dialysis, peritoneal administration of deferoxamine at 10–20 mg/kg per week has been successful in removing aluminum, but, the reported children did not recover fully from the neurological damage. It should be recalled that, when aluminum is chelated with deferoxamine, more free aluminum may go into the CNS and neurological symptoms may actually be exacerbated [64]. Both i.v. and intramuscular deferoxamine administration have also been used successfully to chelate aluminum in adult patients [65]. Often the question is asked whether aluminum-containing antacids are safe in the short term for severe hyperphosphatemia. Animals can become toxic from aluminum in a short period of time. Since aluminum is analogous to lead as far as its toxicity, we should only feel comfortable using aluminum as a phosphate binder if we would be comfortable using lead in the same manner.

In 1991 Salusky et al. [26] showed that $CaCO_3$ was superior to aluminum hydroxide in preventing hyperphosphatemia. Since aluminum causes low turnover bone disease, it does not allow incorporation of phosphate into hydroxyapatite and may actually exacerbate hyperphosphatemia. Hypercalcemia can be avoided by use of a low-calcium dialysate [66].

Calcium acetate may be the ideal phosphate binder in that it binds twice as much phosphate for the same amount of calcium intake [67]. Efficacy is increased if the administration takes place at the same time as food intake. Calcium acetate is unpalatable as a liquid and is not helpful in small children who cannot swallow tablets. Calcium citrate should not be used as a phosphate binder as it enhances absorption of any aluminum that may contaminate the antacid [68].

Summary

Epidemic dialysis encephalopathy and fracturing osteomalacia, which occurred in hemodialysis units in the late 1960s and early 1970s, have now disappeared since safe concentrations of aluminum in dialysate have been established. Encephalopathy, osteomalacia, and microcytic anemia secondary to aluminum toxicity have conclusively been shown to occur in individuals who take aluminum-containing phosphate binders or are exposed to high levels of parenteral aluminum.

I recommend that no child, with or without renal failure, receive aluminum-containing antacids. The Food and Drug Administration should regulate parenteral fluids so that patients receive a total dose comparable to normal environmental exposure. Hyperphosphatemia in renal failure patients should be controlled with phosphate restriction to 10–15 mg/kg per day. When phosphate binders are required, a combination of a low-calcium dialysate and

$CaCO_3$ or calcium acetate as binders has been shown to be safe and effective. If a child inadvertently becomes aluminum toxic, stopping all aluminum exposure is mandatory. Deferoxamine therapy may carry a 30% fatality risk in dialysis patients and should be reserved for those individuals who have severe encephalopathy or bone disease. Since all aluminum toxicity is iatrogenic, it should be avoidable with meticulous medical management.

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Literature abstract

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Growth hormone prevents steroid-induced growth depression in health and uremia

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Treatment with supraphysiological doses of corticosteroids results in protein wasting and impairment of growth, whereas exogenous growth hormone (GH) causes anabolism and improvement of growth. We wanted to know whether the growth depressing effects of methylprednisolone (MP) are more expressed in an organism which is chronically diseased and whether these effects can be counterbalanced by concomitant treatment with recombinant human growth hormone (rhGH). MP in doses from 1 to 9 mg/kg/day caused a dose dependent reduction of length gain, weight gain and weight gain/food intake ratio in 140 g healthy female Sprague-Dawley rats. Food intake was not affected by MP. This points to a change in food metabolism as a mechanism for growth impairment. In addition, treatment with MP inhibited endogenous GH secretion, documented by serum GH concentration profiles over seven hours, decreased IGF-1 serum concentration and disturbed growth cartilage plate architecture. Concomitant treatment with 2.5 to 20 IU/rhGH/kd/day prevented the negative effects of MP on growth in a dose dependent manner and normalized growth plate architecture. In uremic rats in which food efficiency and growth was already reduced, 6 mg MP/kd/day further decreased length gain and prevented weight gain completely by bringing the weight gain/food conversion ratio to the nadir. All effects of MP including reduction of muscle mass could be prevented by concomitant treatment with 10 IU rhGH/kg/day. The effects of MP and rhGH on food efficiency and growth in uremic animals were numerically nearly identical to those in pair fed and ad libitum fed controls, but this may be more relevant in the diseased organism in which basal growth is already suppressed.