Review Article

Susceptibility to Aluminium Intoxication, the Male Gender Bias in Autism, and Implications for Vaccine Risk Screening

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Abstract

Vaccine safety concerns place informed parents into a dilemma: Take the risk of preventable illnesses by refusing vaccines or risk autism by complying with the vaccine schedule. This query sought a resolution by identifying susceptibility factors to intoxication by aluminium, a suspect component used in some vaccines as adjuvants. A systematic review reconciles that although aluminium decreases parathyroid hormone (PTH) secretion, hyperparathyroidism (hPTH) causes susceptibility to aluminium intoxication. The review results incidentally supported a hypothesis explaining the male-biased gender ratio. Thus, a narrative review seemed appropriate on proceeding. Susceptibility extends beyond chronic kidney disease (CKD) to conditions where hypophosphatemia is mediated by hPTH and efficient aluminium excretion is impaired by renal tubular reabsorption. Aluminium intoxication is marked by hypophosphatemia. Thus, individuals with underlying hypophosphatemic tendencies are less able to tolerate aluminium burden. PTH drives aluminium to tissues such as bone and brain as if it were calcium. The male gender bias is explained by a more limited supply of PHEX enzyme (expressed on the X chromosome) that limits phosphate wasting. These findings might imply that aluminium toxicity is sufficient to cause autism. Research is indicated to develop standards for pre-vaccination screening and intervention of conditions that impair aluminium excretion.

Abbreviations: CDC: U.S. Centers for disease control; Al: Aluminium; Al^{3+}: Aluminium cation; Ca^{2+}: Calcium (cation); CaSR: Calcium sensing receptor; Cit^{3-}: Citrate (anion); CKD: Chronic kidney disease; GFR: Glomerular filtration rate; HOL: Hypophosphatemia of leprosy; hPTH: Hyperparathyroidism; PHEX: Phosphate-regulating gene with homologies to endopeptidases, X-linked; PO_4^{3-}: Phosphate (anion); PTH: Parathyroid hormone; XLH: X-Linked hypophosphatemia; ATSDR: Agency for toxic substances and disease.

Introduction

The plausibility that vaccines cause autism requires an explanation why 30 of 31 vaccinated children don't have autism. That explanation is susceptibility. Toxicity is as much a function of susceptibility as it is exposure. Massive media campaigns that downplay the risk of aluminium toxicity, especially in vaccines, have obviated the perception of a need to identify risk factors. But if aluminium is causal, then identifying children at risk before injecting them with aluminium containing vaccines might mitigate the epidemic without compromising public vaccination programs.

The toxic potential of aluminium is indisputable. Aluminium has no biological function in plants, insects, or animals. Its ability to alter biological water dynamics disrupts many biological processes [1]. Aluminium particles in vaccines might be construed as innocuous because they are poorly soluble [2]. However, solvated aluminium cations affect biological structures and processes in micro-molar concentrations by forming complexes with critical oxygen-donor ligands [3]. Aluminium competes with endobiotic cations such as magnesium, calcium and iron [4]. Target ligands include phosphate, citrate, transferrin, calcium sensing receptor (CaSR) and the intracellular calcium transport protein, calmodulin [5-7]. Modern studies show the nexus of acute aluminium toxicity to be impaired gut absorption and renal wasting of phosphate [8-11].

Although aluminium is ubiquitous in the environment, recognized toxicity is fairly uncommon. Nearly all children in the United States are exposed to aluminium in vaccines. Yet, 30:31 children don't have autism [12]. This might be used to dismiss that aluminium causes autism. But assuming aluminium to be causal, the explanation can only be susceptibility due to failed defenses.

Defenses include intact epithelial barriers, limited absorption by the skin and gut and expedient excretion. Aluminium exposures such as during hemodialysis or by injection in vaccines circumvent protective physical barriers making aluminium 100% bioavailable [13]. The final defense is expedient excretion. Aluminium excretion depends upon stable phosphate homeostasis, normal PTH levels and abundant citrate in the glomerular filtrate.

This review investigates the role of PTH in aluminium toxicity and the notion that the risk is not limited to CKD. At the outset, this requires clarifying the confusing dichotomy that PTH is a factor in aluminium toxicity, yet aluminium reduces PTH [14]. Fortuitously, the review also revealed evidence for a male gender bias and susceptibility.

Caution is indicated if disorders of phosphate homeostasis impair aluminium excretion. The risk of the remediation determines the standard of evidence [15]. Thus, given the gravity of autism and the risk-free preventive measures, the evidence presented indicates judicious use and correcting such conditions before elective exposures to aluminium.

Materials and Methods

Purpose

At the outset, a systematic review was intended to reconcile why hPTH is a problem if aluminium decreases PTH. A narrative review seemed appropriate on proceeding to find supporting evidence that hPTH is the susceptibility factor and to explain the gender ratio in autism.

Scope

The review was limited to assessing the effect of disordered phosphate homeostasis on aluminium excretion. An extensive assessment of aluminium distribution to the tissues driven by hPTH exceeds the limitations of this paper. Example disorders of phosphate homeostasis included CKD, primary hPTH, X-linked hypophosphatemia (XLH), hypophosphatemia of leprosy (HOL) and vitamin D insufficiency. The entire differential diagnosis is relevant, but exceeds the limitations of this paper.

Search methods

Many search terms were used such as aluminium parathyroid hormone, hypophosphatemia aluminium toxicity. Google Scholar was the primary search engine. Google AI was useful for quickly identifying primary sources. Forward and backward citation tracking was used.

Criteria for selection of papers

A conscious effort was made to avoid selection bias. Papers were selected for relevance, peer review and propensity to influence clinical practice and health policy. Papers included experimental reports, meta-analyses, case reports and series, reviews and evidence-based hypotheses. Countervailing papers refuting hypotheses were sought and included. Queries with no results were noted. Problematic papers using fallacies were included for discussion. Anonymous articles, speculative hypotheses without testability and superfluous secondary sources were omitted.

Formulation of conclusions

Conclusions were formulated from the standpoint that empirical and rational approaches both have value when taken appropriately. Hypotheses are backed by evidence and are testable.

Results

Systematic review of the relationship between aluminium and parathyroid hormone

Alfrey, et al. (1976): There was significantly higher aluminium content in the bone and brain of CKD patients suffering encephalopathy compared with controls [16].

Significance

This controlled observation implicated aluminium as a necessary cause of emerging encephalopathy among patients receiving hemodialysis. Encephalopathy among non-dialyzed patients proved that low glomerular filtration rate (GFR) was a contributing but not necessary cause. Non-dialyzed patients generally have higher GFRs. Yet, although the aluminium content in tissues was not as high in non-dialyzed patients, it was present in cause sufficient concentrations that were significantly higher than controls. An unknown factor had to be causing aluminium retention in some uremic patients but not others.

Mayor, et al. (1977): The tissue distribution of aluminium in dialysis patients with fatal encephalopathy correlated with the distribution of aluminium in rats fed aluminium after exogenous PTH administration. PTH and tissue aluminium concentrations were highly correlated in deceased dialysis patients [17].

Significance

PTH was identified as a necessary contributor to aluminium retention. Oral aluminium in the presence of hPTH is sufficient to cause aluminium toxicity without kidney disease.

Mayor, et al. (1978): High concentrations of aluminium were found in serum, whole blood and tissues of patients with renal insufficiency. Evidence showed that aluminium is neurotoxic among dialysis patients and suggested the sources can be both oral and parenteral aluminium [18].

Significance

The effect of hPTH may have explained why some dialysis patients exposed to high parenteral aluminium concentrations were developing encephalopathy but others did not.

Mayor, et al. (1980): A controlled experiment using rats with healthy kidneys confirmed a role for hPTH in aluminium toxicity. They fed aluminium to control rats and test rats after administering exogenous PTH. Control rats with normal PTH and fed aluminium did not accumulate any aluminium in brain or body tissues. Test rats fed aluminium after exogenous PTH accumulated significantly more aluminium than controls. Retained aluminium persisted in brain tissues well after oral aluminium was discontinued and until the exogenous PTH was finally withdrawn after ten days [19].

Significance

The Mayor experiment was monumental. The experimental design didn't replicate uremia and secondary hPTH. It replicated primary hPTH. Thus, kidney disease is not a necessary cause for aluminium retention; toxicity can occur in any disorder causing hPTH. Aluminium will accumulate and reside in the brain and body tissues as long as PTH remains high and even after dosages of aluminium are discontinued. Brain aluminium egress did not require a chelating agent. Residual brain aluminium may dissipate when PTH returns to normal, but not before causing significant injury and creating a histological mystery how it happened. Finally, aluminium absorption, distribution and excretion are under hormonal influence.

Alfrey, et al. (1980): Aluminium tissue concentration was measured in 123 cadavers. The cadavers included a control group, a group of non-dialyzed uremic patients who died of something else and a group of dialyzed patients who died of renal encephalopathy. The control tissues had low aluminium concentrations. Aluminium concentrations were increased in the bone and liver of most uremic non-dialyzed patients and increased in all tissues of every dialysis patient who died of renal encephalopathy [20].

Significance

Encephalopathy may occur when rapid aluminium loading exceeds the rate at which bone sequesters aluminium and the surplus accumulates in the liver and brain [20]. Unbeknownst to them, the rate of aluminium loading may have exceeded phosphate-regulating endopeptidase, X-linked (PHEX) enzyme expression to be discussed later.

Gournot-Wittmer, et al. (1981): Bone aluminium content and distribution were compared between two groups of uremic patients. One group had biopsy-proven osteomalacia with negligible bone resorption. The other group was selected for osteitis fibrosa without mineralization defects. They concluded that aluminium may induce vitamin D-resistant osteomalacia only in the absence of severe secondary hPTH. PTH may be involved in aluminiuminduced bone mineralization defects [21].

Significance

Hormonal influence on aluminium distribution and excretion was well established by this time.

Mayor, et al. (1981): Varying aluminium in the potable water supply could account for sporadic local outbreaks of dialysis encephalopathy. On review of prior papers, they wrote that aluminium intoxication may be a function of several disease processes converging to a common clinical presentation. One of the disease processes mentioned was phosphate depletion [22].

Significance

The paper indicated an emerging awareness that preexisting hypophosphatemia is a risk factor. They cited a seminal letter from Pierides, et al. (1976) published in the lancet that implicated preexisting hypophosphatemia as a risk for aluminium intoxication [23].

Mayor et al. (1983): The authors wrote explicitly that considerable evidence argues against the concept that tissue aluminium accumulation occurs as a simple consequence of renal failure.

Significance

The specific mechanisms of toxicity were not completely understood. However, they recognized that other factors besides impaired renal function contribute to aluminium toxicity in CKD [24].

Burnatowska-Hledin, et al. (1983): Smaller exposures to aluminium than what occur during CKD treatment such as in the diet and medications are a cause for concern. Impaired renal function is not necessary for aluminium retention and toxicity.

Significance

They issued a prescient warning about the likelihood that toxicity can occur in populations other than those with renal disease [25]. They probably resolved the autism epidemic before it ever happened. The full text of this paper cannot not be located. But the abstract withstands as evidence that the warning was issued.

Cannatta, et al. (1983): They followed 25 patients on a dialysis unit accidentally exposed to aluminium in the dialysate. Upon discovery, the average plasma aluminium concentration was increased, calcium was increased and PTH was decreased. Two months later, average plasma aluminium and calcium returned to baseline and PTH increased back to normal. This gave rise to a hypothesis that increased plasma calcium inhibits PTH excretion during aluminium intoxication event [26].

Significance

It's true that hypercalcemia inhibits PTH secretion. But it would also be proven later that aluminium stimulates CaSR which down-regulates PTH secretion inappropriately, regardless of how low plasma calcium concentration may be [27]. Their finding indicated awareness that aluminium decreases PTH only after the injurious toxic effects have commenced.

Morrissey, et al. (1983): Application of aluminium to bovine chief cells directly inhibited parathyroid secretion. The investigators didn't know how this happens [27].

Significance

It was clearly evident that aluminium inhibits PTH secretion inappropriately during states of hypophosphatemia.

Reconciling the aluminium-PTH dichotomy

The papers referenced above tell us the following: (1) Aluminium toxicity ensues before it reaches a sufficient concentration to inhibit PTH secretion; (2) Aluminium decreasing PTH is not encouraging. In fact, it may be an ominous sign of increasing toxicity. Although aluminium inhibits PTH secretion, it does so inappropriately; (3) Aluminium toxicity is primarily a phosphate wasting disease; (4) Hypophosphatemia prevails throughout the event, even after aluminium impairs PTH secretion.

Burnatowska-Hledin, et al. (1985) reconciled the PTH-aluminium dichotomy. Plasma aluminium inhibits phosphate reabsorption by the kidneys regardless of PTH, plasma pH and cyclic AMP influence, but more likely due to pre-existing phosphate concentration [10]. The investigators did not have as much information available on phosphate homeostasis as we have today. But they did know that aluminium was inhibiting PTH

secretion inappropriately during a phosphate wasting event. Aluminium uncouples physiological parathyroid feedback control on plasma phosphate and calcium concentration. Any hope of maintaining calcium by way of higher PTH diminishes when aluminium inhibits PTH secretion. Aluminium reducing PTH secretion, a consequence of a deepening state of toxicity, could result in hypocalcemic seizures. The early pioneers didn't know about fibroblast growth factor 23 (FGF23) and PHEX enzyme. The old school taught that PTH was directly responsible for regulating phosphate excretion [28]. They could not have known before 2000 that FGF23 exists, before 2004 that FGF-23 is the primary regulating hormone for phosphate excretion and before 1995 that PHEX enzyme inhibits phosphate over-excretion [29-31]. But they knew enough to avoid using aluminium.

Ultimately, the discovery of CaSR in 1993 and subsequent studies on the effect of aluminium on CaSR confirmed how aluminium decreases PTH [32]. Aluminium is a weak agonist for CaSR. Aluminium stimulates CaSR as if it was calcium, which inhibits PTH secretion. PTH suppression by aluminium is dosage dependent. It suppressed PTH secretion at a higher concentration in chief cell cultures than what is minimally sufficient to achieve toxicity [6]. Aluminium also decreased PTH synthesis in rats, but perhaps not as significantly as it stimulates CaSR to inhibit PTH secretion inappropriately [33].

Aluminium toxicity and phosphate wasting

Aluminium toxicity is primarily a phosphate wasting event

Many authors recognize that phosphate binding with aluminium in the gut can cause hypophosphatemia due to limited absorption. But few papers cover hypophosphatemia due to renal wasting after aluminium injection. A couple of papers reported that after infusion alone, aluminium reduces phosphate concentration [8,10]. Aluminium might inhibit phosphate conservation by way of renal tubular reabsorption due to inadequate phosphate required for oxidative phosphorylation that, in-turn, powers reabsorption [8].

Oral aluminium reduces plasma phosphate by forming insoluble complexes with phosphate in the gut that the gut can't absorb. Conversely, plasma aluminium is likely to be excreted in similar fashion by forming insoluble complexes with phosphate in the renal tubules that the tubules cannot reabsorb.

Despite strident proclamations of aluminium safety, there were no published papers found that entertain the influence that injected aluminium has on renal phosphate handling during pre-existing states of hypophosphatemia. But from what we can glean from existing papers, efficient aluminium excretion requires an ample supply of phosphate whether hypophosphatemia is preexisting or made worse by aluminium infusion.

Hypophosphatemia as a susceptibility factor in autism would necessarily be pre-existing. That, coupled with decreased phosphate absorption after normal dietary aluminium exposures and increased phosphate wasting by the kidneys enhances susceptibility following inter-muscular or intravenous aluminium administration.

Over-treatment of hyperphosphatemia in CKD

Hypophosphatemia has been known as the central feature of aluminium toxicity for a century [34]. Considering the severity of hyperphosphatemia in CKD patients, the idea that over-treatment with oral aluminium is possible demonstrates the power of ingested aluminium to cause hypophosphatemia.

Only a few papers reported hypophosphatemia in uremic patients due to over-treatment. Lichtman, et al. (1969) reported on a case of hypophosphatemia after oral aluminium gel ingestion in a uremic patient [35]. King, et al. (1981) recognized that over-treatment in CKD may cause hypophosphatemia [36]. Andreoli, et al. (1984) found in a case series that non-dialyzed uremic infants are especially susceptible to toxicity after oral administration [37]. The revised practice of avoiding aluminium while treating CKD during the early 1980s may have obviated the need for further research on over-treatment of hyperphosphatemia in CKD.

Phosphate loss in healthy populations

The literature is replete with papers about aluminium-induced hypophosphatemia in healthy people after oral exposure. For example, Dent and Winter (1974) reported on a case of hypophosphatemia causing symptomatic osteomalacia following excessive aluminium antacids in an otherwise healthy patient [38]. Since then, many case reports too numerous to mention describe aluminium intoxication in healthy people following use of aluminium containing antacids.

Discussion

The purpose at the outset of this query was to reconcile why PTH is associated with aluminium retention, yet aluminium decreases PTH in patients with uremia. The preceding review resolved that question and established that aluminium toxicity is a phosphate wasting disease. But the review also opened a floodgate of compelling information further implicating aluminium in autism causation. A narrative review seemed more appropriate upon proceeding.

The discussion takes a macro view of aluminium toxicity, an assessment of phosphatropic and calciotropic hormonal influence on aluminium excretion. An extensive review of PTH control on aluminium trajectory to the tissues exceeds the scope of this paper. But a brief discussion later

5

may provide insight on the poorly understood aluminium flux across cellular membranes [39]. The distribution of PTH receptors seems to determine aluminium trajectory to the tissues during a toxic event.

But first, pre-existing hypophosphatemia is synergistic with renal aluminium retention [10]. Aluminium perpetuates hypophosphatemia, hypophosphatemia perpetuates aluminium retention and a vicious circle ensues. Hypophosphatemia acidifies the plasma [40,41]. Lower plasma pH increases citrate reabsorption in the proximal convoluted tubules [42,43]. As citrate is metabolized, aluminium uses phosphate as a secondary chelator, sacrificing even more phosphate. Aluminium then becomes available for reabsorption in the loop of Henle [11,44]. Rising plasma aluminium reduces the rate of aluminium filtration [11].

There are many other causes of acidosis and hypocitraturia that might impair aluminium excretion. Acidosis need not to be present for hypocitraturia to occur. Hypocitraturia can also be caused by CKD, diarrhea, malabsorption, excessive exercise, ketogenic diets, hypokalemia, high salt diet, several medications and other causes [45]. These and the many causes for acidosis may all be risk factors for endemic aluminium intoxication. But the run-away risk factor for epidemic aluminium intoxication that we may have been calling autism would be hypophosphatemia secondary to vitamin D insufficiency.

## A Novel hypothesis explaining the male gender bias and susceptibility to aluminium toxicity

Disorders of phosphate homeostasis

Disruptions in the hormonal control of phosphate homeostasis underlie susceptibility to aluminium toxicity and the male gender bias. Normal phosphate homeostasis is illustrated in **Figure 1**. Five disorders that cause persistent hypophosphatemia were selected for review later. The association between disorders of phosphate homeostasis and autism is well established [46,47]. These disorders may be preexisting and become worse as aluminium leaches from adjuvant particulates after repeated vaccine injections [48]. An underlying tendency towards hypophosphatemia may render a child susceptible to aluminium toxicity after dosing that is well tolerated otherwise.

Normal excretion of aluminium

Normal aluminium excretion requires citrate and phosphate in the renal tubules. Aluminium is carried mostly by transferrin and other proteins and in complexes with citrate and phosphate in the plasma. Citrate is instrumental in shuttling aluminium from transferrin, the primary plasma aluminium transporter, through ligand exchange [49]. Complexes of aluminium with citrate can readily pass through the glomerular filter [4]. Citrate is the primary anion that carries aluminium safely into the bladder with minimal reabsorption [11, 50].
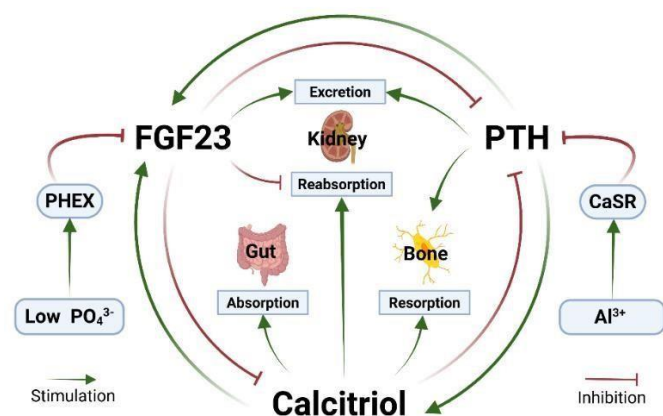
Figure 1: Phosphate homeostasis. Plasma PO_4^{3-} concentration varies normally during dynamic metabolic states. Minimum PO_4^{3-} concentration is a function of PTH and/or calcitriol effect on kidney reabsorption and bone or gut to absorb PO_4^{3-} into the plasma. FGF23 acts on the kidneys to excrete PO_4^{3-} when it's high. PHEX enzyme checks FGF23 to prevent over-excretion preventing hypophosphatemia [51]. Al^{3+} stimulates CaSR inappropriately to inhibit PTH secretion. **Note:** Al^{3+}: Aluminium cation; CaSR: Calcium sensing receptor; FGF23: Fibroblast growth factor-23; PHEX: Phosphate regulating gene with homologies to endopeptidases on the X-chromosome; PO_4^{3-}: Phosphate; PTH: Parathyroid hormone; RTC: Renal tubular cells; Created in BioRender. Kette, S. (2025) https://BioRender.com/tds9db2.

Metabolic acidosis due to hypophosphatemia increases citrate metabolism

The kidney tubules will reabsorb aluminium without adequate citrate in the glomerular filtrate. As plasma phosphate concentration decreases, plasma pH decreases and citrate availability in the renal tubules decreases. **Figure 2** illustrates the function of renal cell handling of citrate during states of metabolic acidosis. Low phosphate supply impairs conversion of adenosine diphosphate (ADP) to adenosine triphosphate

(ATP) which then causes anaerobic metabolism [40]. This causes a drop in plasma pH. Also, metabolic acidosis results because hPTH causes bicarbonate wasting [51].

To compensate for the tendency toward acidosis, the kidney tubules will reabsorb and metabolize citrate. Acid-base balance and expression of the Na^+-dicarboxylate cotransporter control citrate reabsorption in the proximal convoluted tubules [41-43]. Extreme hypophosphatemia causes metabolic acidosis [40, 41]. But hypophosphatemia need not be extreme as plasma pH falls decrementally and may be compensated during the process. Nevertheless, citrate is less available to chelate aluminium efficiently in the glomerular filtrate when PTH is sufficiently high.

Aluminium needs another anion to remain solvated if citrate is metabolized

Although citrate dominates phosphate in the competition for aluminium binding [5], aluminium excretion requires phosphate in the glomerular filtrate as a backup chelator. Once in the filtrate, aluminium can form insoluble complexes with phosphate that the tubules don't reabsorb. Normally, aluminium phosphate is a component of the amorphous sediment seen on microscopic examination during urinalysis [52]. But if plasma phosphate concentration is too low, then phosphate concentration in the glomerular filtrate is too low [53]. If both phosphate and citrate are insufficient, anions fixed to calcium transporters on renal cells may be the only ligands remaining to attract aluminium. Ultimately, aluminium reabsorption happens in the loop of Henle [11, 44,50].

Reasoning that supports the notion that phosphate escorts aluminium to the bladder as a secondary chelator is based on the principle by which oral aluminium binds with phosphate in the gut. But in the kidney, precious phosphate is excreted as aluminium phosphate, thus being sacrificed for the noble cause to excrete aluminium. The costly tradeoff is a nudge favoring the deepening state of hypophosphatemia.
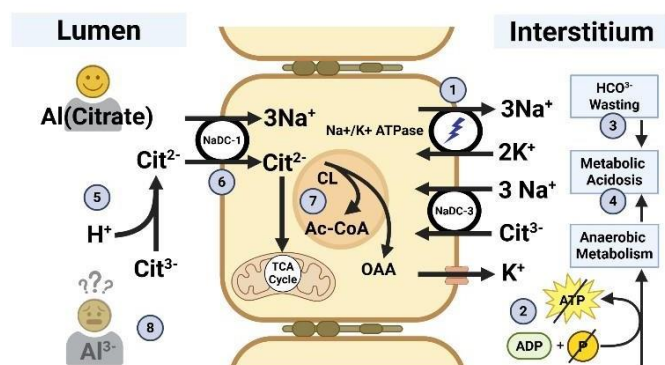
Figure 2: Renal tubular cell handling of citrate in response to low phosphate and metabolic acidosis. 1: The Na^+/K^+ ATPase pump powers the system by creating an electrochemical gradient that facilitates Cit^{2-} entry into the cell; 2: Low phosphate impairs conversion of ADP to ATP causing anaerobic metabolism [40]; 3: hPTH causes renal HCO_3^- wasting [51]; 4: Lactate and α-β-hydroxybutyric acid accumulate [40]; 5: H^+ surplus favors Cit^{2-}; 6: Na^+-dicarboxylate cotransporter transfers Cit^{2-} into the cell; 7: Intracellular Cit^{2-} metabolism [42,43]; 8: Cit^{3-} is unavailable to escort Al^{3-} to the bladder for safe excretion. **Note:** Ac-CoA Acetyl CoA; ADP: Adenosine diphosphate; Al^{3-}: Aluminium cation; ATP: Adenosine triphosphate; Cit^{2-}: Citrate anion in dicarboxylate form; Cit^{3-}: Citrate anion in tricarboxylate form; CL: Citrate lyase; H^+: Hydrogen/proton; HCO_3^-: Bicarbonate; hPTH: Hyperparathyroidism; K^+: Potassium; Na^+: Sodium; NaDC: Sodium/dicarboxylate cotransporter; Na^+/ K^+ ATPase: Sodium-potassium pump; OAA: Oxaloacetate; phosphate - Phosphate; TCA: Tricarboxylic acid; Created in BioRender. Kette, S. (2025) https://BioRender.com/v3s49lm

Demand for PHEX enzyme to stop phosphate wasting exceeds the rate of expression

The basis of the hypothesis for a male gender bias in aluminium toxicity is that the high demand for PHEX enzyme imposed by low plasma phosphate concentration exceeds the rate of supply. PHEX enzyme takes time for synthesis. There was no evidence found that osteocytes hold sufficient PHEX enzyme in storage. It is more likely expressed on demand. If the demand exceeds the rate of expression, then FGF23 remains disinhibited and inappropriate phosphate excretion may increase. Subsequently, plasma pH decreases, renal citrate resorption and metabolism increase, normal aluminium chelation with citrate decreases, phosphate is sacrificed and aluminium becomes more available for reabsorption.

The X-linked female protective effect

There is nothing novel about a possible female X-linked causal effect in autism. Mendes, et al. (2025) entertained the possibility. They proposed several candidate genes including FGF23. But it is more conceivable that FGF23 mutations would cause hyperphosphatemia. Although they didn't identify PHEX, autism is associated with hypophosphatemia [46, 47].

PHEX enzyme supply is more limited in boys because PHEX gene is located on the X chromosome. Off-handed reasoning that suggests girls have a double dose of PHEX gene expression holds true. Lyonization is a process during female embryonic development where the redundant X

7

chromosome is deactivated to prevent double X gene dosing. But not all genes are fully Lyonized [54]. The PHEX gene is among those that variably escape Lyonization in girls [55].

The duplicated PHEX gene may have undergone more complete Lyonization in vaccinated girls with autism, whereas, the duplicated PHEX gene may have escaped Lyonization in fully vaccinated girls without autism. This could be tested using unaffected fully vaccinated girls as a control group, however it would be difficult to control for aberrant phosphate homeostasis that may have occurred during the earlier years of the child's life.

HOL provides evidence that the supply of PHEX enzyme in girls is more abundant than in boys. Girls would be more able to satisfy the high demand for PHEX enzyme created when aluminium exposure and pre-existing hypophosphatemia converge. This may very well explain the gender bias in autism.

The CDC reported that the gender ratio in autism decreased from 4.2:1 in 2018 to 3.8:1 in 2022. They attributed the converging gender ratio to improved identification in girls [12]. On the other hand, if convergence of the gender ratio is attributed to increasing aluminium exposure, this would be consistent with the hypothesis that the demand for PHEX enzyme exceeds the rate of supply. Increasing aluminium exposures may eventually overwhelm the X-linked female protective factor in more girls. The gender ratio could converge to 1:1 as prevalence approaches 100% if aluminium exposures continue to increase.

Other factors can inhibit PHEX expression

Other factors may compound the problem of limited PHEX enzyme expression. They include but may not be limited to hPTH, activated vitamin D [56] and tumor necrosis factor-alpha (TNF-α) [57]. This opens Pandora's box of risk factors for phosphate wasting. TNF-α is an inflammatory cytokine that is increased in viral and bacterial infections. Aluminium itself induces TNF-α secretion [58]. Maybe pediatricians should wait until sick children are well before injecting them with aluminium. Any mechanism for inhibition of PHEX enzyme expression probably increases susceptibility to aluminium intoxication.

The remainder of this paper provides further explanations, evidence and citations supporting this hypothesis and why it was missed. It is tedious but necessary to review selected disorders of phosphate homeostasis and aluminium toxicity. There are many others too numerous for review here.

Selected disorders of phosphate homeostasis

Acquired and genetic disorders of phosphate homeostasis may alter the toxicokinetics of aluminium. Disorders selected for focused review include CKD, primary hPTH, XLH, HOL and vitamin-D insufficiency. **Table 1** summarizes them. HOL is omitted from **Table 1** because data is insufficient due to it being such a rare disease.

Chronic kidney disease

CKD patients on dialysis were especially prone to aluminium toxicity during the early 1970's. It was termed, dialysis dementia before aluminium in the dialysate solution was found to be the cause. Like autism, speech loss was a common presenting symptom. Patients were reported to express frustration with the loss of speech and inability to communicate before the disease progressed to dementia [59].

Authors casually writing about aluminium safety often remark that CKD patients are the only individuals at risk for aluminium toxicity. They typically presume that toxicity is caused by aluminium not passing the glomerulus. But aluminium is small enough that it easily passes through the glomerulus [11]. Phosphate, however is retained because it is a large molecule and significant nephron loss in kidney disease. Aluminium does not pass the glomerulus as readily because of its attraction to unfilterable phosphate and other high molecular mass complexes which are trapped in the plasma. Plasma citrate facilitates aluminium passing through the filter in such case [49], where aluminium then becomes available for excretion or reabsorption in the loop of Henle [11, 44, 50].

Unlike the other disorders selected for review, CKD causes hyperphosphatemia. PTH becomes elevated as the result of hypocalcemia in CKD. There is evidence, however, of hypophosphatemia occurring in CKD due to over-treatment with aluminium used as gut phosphate binders as mentioned earlier. It is possible in these cases that aluminium induced hypophosphatemia seen in CKD was reducing plasma pH, increasing citrate reabsorption and eliminating citrate as a chelator to escort aluminium to the bladder. Hypocitraturia is common in CKD and may actually be the primary problem that causes aluminium retention in some of these patients [60].

| | PTH | FGF-23 | Calcidiol | Calcitriol | Plasma | | Urine | |
					Ca^{2+}	PO_4^{3-}	Ca^{2+}	PO_4^{3-}
Primary hPTH	H†	H	L to N	N to N^{+}	H	L to N	H	H

XLH	N to H	HH†	N	N to L¹	N	LL	L	L
Low Vit D	H	L	L†	L	L	LL	L	L o N
CKD	H	H	L to N	L	N	HH†	LL	N to H³

Note: †: Denotes the primary driver of the disorder; 1: Inappropriately N or L despite low PO_4^{3-}; 2: Can be L to N due to bone Ca^+ resorption to maintain plasma concentration; 3: N to H in urine only because plasma PO_4^{3-} is exceptionally high.

Table 1. Sample disorders of PO_4^{3-} homeostasis that may confer risk of aluminium retention and toxicity.

Note: Concentrations are qualitative generalizations that may not apply uniformly to individuals. Abbreviations: Ca^{2+}: Calcium; CKD: Chronic kidney disease; FGF23: Fibroblast growth factor-23; hPTH: Hyperparathyroidism; PO_4^{3-}: Phosphate; PTH: Parathyroid hormone; XLH: X-linked hypophosphatemia.

There is no report of a male gender bias in aluminium toxicity due to CKD. This should be expected because aluminium excretion is impaired due to poor filtration. Furthermore, unlike impaired excretion due to renal tubular reabsorption, there is no call for PHEX enzyme to inhibit FGF-23 during a state of hyperphosphatemia. There is evidence of a link between kidney disease and developmental disabilities, autism and unspecified behavioral changes [61-63].

Primary hyperparathyroidism

The underlying problem in primary hPTH is inappropriate PTH secretion. It is caused by parathyroid gland tumors and hyperplasia [64, 65]. It can be caused by several other problems, for example, mutation of the gene that expresses CaSR [66]. Mayor, et al. (1980) actually reproduced primary hPTH using exogenous PTH in healthy rats when performing the landmark experiment to ascertain the role of PTH in uremic patients with aluminium toxicity [19]. This experiment proved that CKD is not the only disease that predisposes people to aluminium toxicity. PTH in excess by any means causes hypophosphatemia and hypercalcemia. PTH acts directly on proximal convoluted tubules and to some degree, indirectly by prompting FGF23 to inhibit phosphate reabsorption [64, 65, 67, 68]. Primary hPTH is rare in children [69]. There was no information linking it with autism. But it is associated with cognitive impairment and dementia [70].

X-linked hypophosphatemia

This causes X-linked hypophosphatemic rickets. The primary driver in XLH is uninhibited FGF23. The PHEX gene expresses PHEX enzyme [31]. PHEX enzyme inhibits FGF-23 normally when plasma phosphate concentration subsides to a desirable concentration [51]. In XLH, mutations in the PHEX gene cause poor quality or absent PHEX enzyme expression [31, 71]. FGF-23 is uninhibited in XLH resulting in hypophosphatemia.

A demographic study of 579 XLH patients found that 64% were female [72]. Other papers report no differences in severity based upon gender [73,74]. This might weaken the hypothesis off-hand. However, a series of 38 radiologic examinations of untreated adults showed men to be more severely affected by bone changes [75]. The genotype of XLH does not correspond with the severity of phenotype expression in women. The explanation is unclear, but perhaps variable X chromosome inactivation in women and gene dosing is involved [71].

Genetic autism causation enthusiasts should look here. XLH is an X-linked dominant inherited disorder. There is no father to son transmission. There are at least 729 PHEX variants that impart a spectrum of severity in presentation of the disease [71]. XLH isn't a terribly common disorder, so there will not be sufficient data linking XLH and autism. However, there is a case report of XLH wherein the authors hypothesized that 10-15% of autism can be attributable to PHEX gene variants. This estimation was based on the percentage of autism classified genetically as syndromal autism [76].

Hypophosphatemia of leprosy

Like XLH, the driver in HOL is uninhibited FGF23. It is reasonable to believe that the supply of PHEX enzyme in girls can be up to twofold more abundant as previously discussed. The pathophysiology of HOL provides stronger evidence of a limited supply of PHEX enzyme in boys and variably in some girls. HOL is a natural experiment that may help to prove the case. Mycoplasma leprae inhibits PHEX enzyme expression in osteocytes and Schwann cells [77, 78]. The profound hypophosphatemia seen in HOL causes skeletal malformations resulting in a 2:1 gender bias toward males for physical disability [79]. Although Mycoplasma leprae infection is rare, it illustrates the greater potential for PHEX enzyme depletion in boys.

Vitamin D insufficiency

Vitamin D insufficiency must be distinguished from calcitriol insufficiency. Calcitriol is the hormone form of vitamin D. There is a myriad of problems converting vitamin D to calcitriol such as mutated genes that express the necessary enzymes. Also, calcitriol can be plentiful yet ineffective due to abnormal receptor sites. In vitamin D insufficiency, calcitriol is insufficient because there is insufficient vitamin D available to convert [80, 81]. Children with dark skin are at particularly high risk [82]. The prevalence of vitamin D insufficiency is 42.4% of black and 4.2% of white women of child bearing age [83]. This may explain the skewed race ratio in autism [12].

Plasma phosphate concentration is low in vitamin D insufficiency due to reduced phosphate resorption from bone and poor absorption by the gut. Simultaneously, FGF23 remains highly active under excessive PTH stimulation causing inappropriate phosphate excretion when plasma concentration is already low [84]. This is worrisome when aluminium reduces plasma phosphate concentration even more. And when children run low on PHEX enzyme to inhibit FGF23 over-secretion, aluminium toxicity may result. **Table 2** summarizes the proposed causal cascade leading to toxicity.

1. Normal PTH secretion [51] PTH stimulates *CYP27B1* $\uparrow$1α-hydroxylase Normal Al^{3+} body burden 2. Vitamin D insufficiency [80] $\downarrow$ Liver 25(OH)D3 for hydroxylation $\downarrow$ Calcitriol (M<F) Gut $\downarrow$'s Ca^{2+} & PO_4 absorption RT $\uparrow$'s Ca^{2+} & PO_4 reabsorption 3. Plasma trends toward $\downarrow$ $Ca^{2+}$and PO_4^- $\downarrow$ CaSR stimulation $\uparrow$ PTH secretion 4. $\downarrow$'d Calcitriol state continues 5. Secondary hPTH $\uparrow$ PTH stimulation Bone $\uparrow$ FGF23 production & excretion $\uparrow$ Ca^{2+} & PO_4 resorption Rickets (M≥F) Kidney PCT $\downarrow$ PO_4 reabsorption DCT $\uparrow$ Ca^{2+} reabsorption Gut $\downarrow$'s Ca^{2+} & PO_4 absorption RT $\uparrow$'s Ca^{2+} & PO_4 reabsorption 6. $\downarrow$ NL $\uparrow$ FGF23 (population variability) PCT $\downarrow$ PO_4 reabsorption, PO_4 wasting Plasma; $\downarrow$ to NL Ca^{2+} $\uparrow$ PHEX expression (M<F)	7. $\uparrow$ PHEX demand: rickets (M≥F) 8. $\downarrow\downarrow$ PO_4 favors metabolic acidosis 9. $\uparrow$ Cit^{3-} reabsorption in PCT Some Al^{3+} reabsorption, impaired excretion 10. Stable state of hypovitaminosis D $\uparrow$ PTH $\downarrow\downarrow$ PO_4 $\downarrow$ to NL Ca^2 11. $\uparrow$ Aluminium body burden $\downarrow\downarrow$ PO_4^- in plasma is worse PHEX demand increases Plasma pH trends even lower $\downarrow\downarrow$ Cit^{3-} in PCT $\downarrow\downarrow$ PO_4^- in glomerular filtrate $\uparrow$ Al^{3+} reabsorption in LOH 12. PTH distributes Al^{3+} to body tissues/brain 14. Al^{3+} toxicity ensues 13. Al^{3+} stimulates CaSR $\downarrow$'d PTH (inappropriate) 15. Underlying $\downarrow$ calcitriol persists 16. $\downarrow$ PTH support for plasma Ca^{2+} & PO_4^- $\downarrow\downarrow\downarrow$ PO_4^- PHEX depletion (M>F) $\uparrow$ Nudge toward acidosis $\uparrow\uparrow$ PCT Cit^{3-} reabsorption No Al^{3+}chelation in tubules Significant Al^{3+} reabsorption at LOH 17. Permanent injury by Al^{3+} toxicity 18. Autism epidemic.

Table 2: Proposed cascade leading to aluminium toxicity in children with Vitamin D insufficiency.

Note: Proposed cascade of events predisposing to aluminium retention and toxicity; PTH: Parathyroid hormone; Al^{3+}: Ionized aluminium; CYP27B1: Cytochrome P27B1; 25(OH)D3: inactive form of Vitamin D; Ca^{2+}: Ionized calcium; CaSR: Calcium sensing receptor; hPTH: Hyperparathyroidism; Cit^{3-}: Citrate anion; PCT: Proximal convoluted tubule; DCT: Distal convoluted tubule; RT: Renal tubule; FGF23: Fibroblast growth factor; PHEX: Phosphate regulating gene with homologies to endopeptidases on the X-chromosome; LOH: Loop of henle.

Although any disorder of calcium and phosphate homeostasis may confer the risk of aluminium toxicity, vitamin D insufficiency is the *sine qua non* for the autism epidemic. Innumerable papers cover the link between autism and vitamin D insufficiency. Pioneers in this research led by Grant and Cannell have recognized the strong link between vitamin D insufficiency and autism [85-90]. Their work highlights observations that U.S. autism exceptional student educational enrollment rates are generally higher among less sun exposed populations such as those in northern states.

Is aluminium distribution to the tissues determined by parathyroid hormone receptors?

Although the primary focus of this paper is the synergy between aluminium and preexisting disorders causing hypophosphatemia, the value of assessing the distribution of aluminium to the tissues might provide evidence of the role that PTH plays in aluminium retention and toxicity. Not only are hypophosphatemia, acidosis, hypocitraturia and aluminium retention downstream effects of hPTH, PTH seems to alter aluminium trajectory to the tissues according to the distribution of PTH receptors.

Bago, et al. (2008, 2009) identified locations in the brainstem of PTH2 receptors [91, 92]. The distribution of PTH2 receptors may reflect the mapping of brainstem deficits observed clinically in autism cases as described by McGinnis, et al. (2013) and others [93-96]. The manner in which calcium enters the brain might also explain how aluminium enters the brain and we know that it does [97,98]. Exley and Mold (2013) provide excellent insights on how this might happen [39].

The very fact that PTH drives aluminium to the brain [19] and other tissues suggests that aluminium follows calcium channels under PTH control [4]. PTH is the master hormone for calcium homeostasis and the driver of calcium to the cells. There is also evidence that aluminium may follow iron pathways after being carried by transferrin [4, 13]. But PTH isn't known to mediate iron transport.

There are a few PTH/calcitriol-controlled calcium transport channels that are candidates for hijacking by aluminium. Store-operated calcium entry is a PTH controlled calcium pathway [99]. Calcitriol, when activated by PTH, mediates paracellular transport of calcium across tight junctions [100]. PTH action to convert vitamin D to calcitriol activates endothelial transient receptor potential vanilloid 5 (TRPV5) and TRPV6 [101]. These TRPV channels may mediate aluminium flux across gut epithelium [102], thick ascending limb of the loop of Henle and distal convoluted tubules [68]. Aluminium must necessarily pass through TPRV6 calcium channels in order to interact with calmodulin, an integral part of this mostly ion specific channel [7].

TPRV5 and TPRV6 are thought to be highly calcium specific [103]. However, over-expression can lead to cadmium and zinc toxicity [104]. Peng, et al. (1999) used xenopus oocytes to determine whether other cations can pass into the TRPV6 gateway. Sodium, calcium and barium can pass. Other ions tested included magnesium, gadolinium, lanthanum, iron, copper, lead cadmium, cobalt, zinc and nickel [105, 106]. Aluminium was not tested. There was no other evidence found that proves trans-cellular gateways for aluminium. However, literature search did reveal that a xenopus is a water frog, with claws [107].

How it was missed

The ADME acronym

ADME is a teaching tool used in toxicology and pharmacology to impress upon students the rigid requirement to evaluate every one of absorption, distribution, metabolism and excretion of a substance. The aluminium debate and the bulk of messaging on aluminium safety focuses only on administration (which also entertains the degree of exposure). The need for attention to safe excretion has been neglected.

Administration and dosage; proof of safety

The notion that aluminium in vaccines has been proven safe merely by claims of low dosing and the ostensible lack of evidence of any harm violates logic because an absence of evidence proves nothing [108]. In this case, establishment vaccine scientists claim aluminium has been proven safe for one and all based simply on low exposures. Never mind susceptibility. Keith, et al. (2007) reviewed aluminium toxicokinetics in childhood vaccines with an implicit assumption that aluminium is always safely excreted [109]. Mitkus, et al. (2013) proclaimed the childhood vaccine schedule to be universally safe based upon minimum risk levels derived from adult data. There were no exceptions considered for individuals susceptible to aluminium toxicity [110].

Lyons-Weiler and Ricketson (2018) is the most outstanding paper that enumerates aluminium body burden imposed upon children by the vaccine schedule. It considers a child's body weight in calculating a more realistic minimum risk level of aluminium in pediatric vaccine practice [111]. McFarland, et al. (2020) assessed infant aluminium exposure through vaccines and environment. The CDC recommended vaccine schedule alone exceeds safe exposure levels, environmental exposure notwithstanding [112]. While the modes of administration and degree of exposure are exquisitely relevant, aluminium metabolism and excretion are also important because therein lies the susceptibility.

Metabolism and excretion; evidence ignored

The reassurance of safety based on absence evidence requires not looking, ignoring evidence to the contrary, or low research testing sensitivity [108]. The lack of attention to aluminium distribution and excretion is amazing considering its extensive use in vaccines, medicines and cosmetics. Noteworthy papers on the safety profile of aluminium are available on-line and are quite comprehensive. The U.S. Agency for Toxic Substances and Disease Registry's (ATSDR) most recent update bears a review on susceptibility to infections after aluminium exposure and children's susceptibility to toxins in general. ATSDR did not address metabolic or genetic susceptibilities to aluminium intoxication [113]. Krewski, et al. (2007) did cite papers supporting that people with CKD, pregnancy and premature birth are at higher risk due to impaired excretion [114]. But there were no papers found that specifically address disorders of phosphate homeostasis as susceptibility factors except that of kidney disease. Some authors may infer that aluminium toxicity in CKD is caused by it's not passing through the glomerulus making it the only risk factor. This is simply incorrect. The truth is that any disorder with high PTH and hypophosphatemia confers susceptibility.

The unheeded warning

The lion's share of papers on the PTH-aluminium link emanated from Michigan State University. In the hallmark paper, Burnatowska-Hledin, et al. (1983) wrote explicitly that smaller exposures than what occur during CKD treatment such as in the diet and medications are also causes for concern, that impaired kidney function is not necessary for aluminium retention and toxicity. They explicitly warned about the likelihood that toxicity can occur in populations other than those with renal disease. As noted earlier, they probably solved the mystery of the autism epidemic long before it happened. Efforts to locate that paper were futile, including contacting the lead author. Nonetheless, the abstract is irrefutable evidence that the warning was issued [25].

But the warning continues to be ignored. Heretofore, a commonly quoted justification for unlimited use of aluminium in vaccines is as follows: The widespread use of aluminum adjuvants can be attributed in part to the excellent safety record based on a 70-year history of use. [115]. This logic, based on *circulus in probando*, reads that aluminium is safe because we use it a lot and we use it a lot because it is safe [116]. This works

11

as long as we comply with the implicit requirement to dismiss valid evidence of risk as theoretical concerns [117]. Industry scientists recently reiterated their intent to use aluminium into infinity and beyond without limitations or precautions using the same line of reasoning [118].

Susceptibility must be considered in population study designs

Andersson, et al (2025) collected data on 1.38 million vaccinated Danish children to assess hazard ratios for several autoimmune, allergic and neurodevelopmental outcomes. They divided the vaccinated children into exposure groups distinguished from each other by 1 mg increments of injected aluminium by the age of two years. They averaged the hazard ratios between adjacent groups. This methodology failed to detect concerning hazard ratios. They did not calculate the hazard ratio between the lowest and highest dosage groups [119]. However, even that could have failed to demonstrate increased risk in the high dose groups because susceptibility factors might place children in the low dose groups at equal risk. The study design lacked any accounting for susceptibility. Yet, lay and social media pundits echoed the conclusion that aluminium was proven to be safe for one and all.

Forty years ago, when medical practice was controlled by physicians, nephrologists had sufficient evidence and the wisdom to stop using aluminium in uremic patients. They did not need to prove the Michaelis-Minton constant for aluminium and calcium transport protein in xenopus oocytes [105]. Physicians must assert control of their practices once again and resume treating individuals instead of populations.

Limitations of vaccine risk screening

It is important to consider that pre-vaccination screening may have limited benefits. First, aluminium has a bi-modal mechanism of toxicity. It has direct toxic effects such as that seen in CKD and perhaps immediately following a battery of childhood vaccines. It is also immunotoxic where autoimmunity may result [120, 121]. A given aluminium load may not precipitate symptoms of acute toxicity yet be sufficient to cause delayed autoimmunity or allergies. As for inducing immunotoxicity, there may be no safe level of exposure. Risk screening will merely prevent acute toxic effects in susceptible babies.

Second, most neonates have physiologically high PTH within 24 hours of birth, peaking at seven days and gradually decreasing until plasma calcium, phosphate and calcitonin normalize [122]. In Movsas, et al (2013), the investigators measured aluminium in the urines of 15 pre-term infants after their two-month vaccinations and found there to be no aluminium. Although they considered this finding to be reassuring [123], the finding is actually alarming. It means that preterm infants don't excrete aluminium at two months of age. Therefore, pre-screening newborns would be fruitless because most of them probably would not meet criteria for safe vaccination. Fortuitously, the U.S. Advisory Committee on Immunization Practice recommended softening the recommendation for the aluminium containing hepatitis B birth dose albeit with insufficient data, recognized evidence of harm, or any discussion of vaccine risk [124].

Finally, pre-natal aluminium antacids, maternal dietary aluminium, aluminium containing vaccines and post-natal dietary aluminium exposure may be cause sufficient among susceptible populations. Pre-vaccination screening of babies would not prevent these exposures.

Conclusion

This review explicates the hypothesis of a male gender bias and susceptibility to aluminium toxicity. Disorders of phosphate homeostasis probably confer risk at exposure levels that are otherwise well tolerated. Girls are likely to be protected by their ability to express more PHEX endopeptidase on the duplicate X chromosome whereas boys only have one X chromosome. Nevertheless, efforts to identify environmental causes of autism should continue regardless of how compelling this hypothesis may be.

The risk of aluminium toxicity extends beyond that of chronic kidney disease

CKD is currently the only recognized risk factor for aluminium toxicity due to limited filtration of aluminium bound by phosphate in the plasma. But susceptibility to aluminium toxicity extends beyond that caused by kidney disease. hPTH by any other means can impair aluminium excretion due to reabsorption of filtered aluminium. In either case, hPTH drives retained aluminium to body tissues. However, some early paper titles appear contradictory because aluminium also reduces PTH. The dichotomy leads to a hasty dismissal that hPTH has a role in aluminium toxicity. In fact, aluminium reducing PTH during an intoxication event may be ominous. A systematic review of literature to resolve the contradiction incidentally revealed compelling evidence that might explain the autism epidemic better than increased awareness. Any preexisting disorder with hPTH, subsequent phosphate wasting, metabolic acidosis, or hypocitraturia probably confers susceptibility. Hypophosphatemia is a hallmark of aluminium toxicity. Low phosphate concentration acidifies the plasma which, in-turn, increases citrate reabsorption by the kidney tubules. But citrate is the primary aluminium chelator in the glomerular filtrate. As citrate is metabolized, aluminium reabsorption increases in the loop of Henle. Ultimately, PTH receptor distribution determines the trajectory of retained aluminium to the tissues during an intoxication event.

The male gender bias and limited PHEX enzyme expression

The male-biased gender ratio in autism may be explained by a more limited supply of the enzyme expressed by the PHEX gene. PHEX enzyme is required to limit phosphate wasting. If the duplicated PHEX gene in girls variably escapes inactivation, then expression of PHEX enzyme confers

a protective effect in most, but not all girls. The hypothesis of susceptibility and the reason for the gender ratio presented herein is consistent with the model that autism has environmental causation with genetically mediated susceptibility.

Vitamin D insufficiency may explain the demographic features of autism

Vitamin D insufficiency, the second most common cause of secondary hPTH, would be the *sine qua non* for the autism epidemic. This is illustrated by a higher prevalence of autism among non-white children and those living in less sun exposed climates.

Limitations and significance of this review

Although this paper might contribute to the conclusion that aluminium is a sufficient cause for the autism epidemic, it does not stand alone as a justification to conclude that aluminium containing vaccines are the sole cause [15]. Aluminium exposures according to the childhood vaccine schedule may be a major contributing cause. But other sources of aluminium can contribute to toxicity. Furthermore, this paper is not a recommendation for or against vaccination practice. Parents are advised to consult with their pediatricians on any concerns about vaccine safety. Vaccines notwithstanding, empirical research on susceptibility to aluminium toxicity and development of pre-vaccination screening standards are needed.

We are years away from safely deploying alternative adjuvants due to the time needed for research and development and safety and efficacy trials. In the meantime, we should not wait while another generation of children incurs the risk of aluminium intoxication unnecessarily. Effective pre-vaccine screening for susceptibility to aluminium toxicity should not obviate the need for continued development of alternative vaccine adjuvants or enable a continuing increase of aluminium burden by expanding the vaccine schedule. To the contrary, eliminating nonessential immunizations during early childhood such as the aluminium containing hepatitis B vaccine will make way for safer administration of the more essential childhood vaccines.

Until more empirical evidence becomes available, the risk of the remedy determines the standard of evidence for causation. The standard of evidence is low because there is no risk in taking these measures to mediate the autism epidemic [15]. Therefore, we should recognize the immediate need to avoid unnecessary aluminium exposure. Where necessary elective use and unavoidable exposures are concerned, prevaccination screening and correcting disorders that confer susceptibility should be considered before proceeding.

The gravity of the problem demands this approach. If the weight of current evidence meets a higher standard that indicates permanent changes in vaccination practice, then pediatricians should never send another afflicted child home with a psychiatric diagnosis.

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Conflicts of Interest

The author declares no conflicts of interest relevant to this research. Assessment of scientific discipline practiced in this query should indicate the risk of bias. Readers should maintain universal awareness of potential non-financial conflicts based upon implicit bias, ideological and religious beliefs, expert testimony, community-based advocacy and private personal relationships with individuals having the disorders under investigation.

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