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Aluminum in Neurological and Neurodegenerative Disease

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Abstract

With continuing cooperation from 18 domestic and international brain banks over the last 36 years, we have analyzed the aluminum content of the temporal lobe neocortex of 511 high-quality human female brain samples from 16 diverse neurological and neurodegenerative disorders, including 2 groups of age-matched controls. Temporal lobes (Brodmann areas A20–A22) were selected for analysis because of their availability and their central role in massive information-processing operations including efferent-signal integration, cognition, and memory formation. We used the analytical technique of (i) Zeeman-type electrothermal atomic absorption spectrophotometry (ETAAS) combined with (ii) preliminary analysis from the advanced photon source (APS) hard X-ray beam (7 GeV) fluorescence raster-scanning (XRFR) spectroscopy device (undulator beam line 2-ID-E) at the Argonne National Laboratory, US Department of Energy, University of Chicago IL, USA. Neurological diseases examined were Alzheimer's disease (AD; $N = 186$), ataxia Friedreich's type (AFT; $N = 6$), amyotrophic lateral sclerosis (ALS; $N = 16$), autism spectrum disorder (ASD; $N = 26$), dialysis dementia syndrome (DDS; $N = 27$), Down's syndrome (DS; trisomy, 21; $N = 24$), Huntington's chorea (HC; $N = 15$), multiple infarct dementia (MID; $N = 19$), multiple sclerosis (MS; $N = 23$), Parkinson's disease (PD; $N = 27$), and prion disease (PrD; $N = 11$) that included bovine spongiform encephalopathy (BSE; "mad cow disease"), Creutzfeldt-Jakob disease (CJD) and Gerstmann-Straussler-Sheinker syndrome (GSS), progressive multifocal leukoencephalopathy (PML; $N = 11$), progressive supranuclear palsy (PSP; $N = 24$), schizophrenia (SCZ; $N = 21$), a young control group (YCG; $N = 22$; mean age, 10.2 ± 6.1 year), and an aged control group (ACG; $N = 53$; mean age, 71.4 ± 9.3 year). Using ETAAS, all measurements were performed in triplicate on each tissue sample. Among these 17 common neurological conditions, we found a statistically significant trend for aluminum to be increased only in AD, DS, and DDS compared to age- and gender-matched brains from the same anatomical region. This is the largest study of aluminum concentration in the brains of human neurological and neurodegenerative disease ever undertaken. The results continue to suggest that aluminum's association with AD, DDS, and DS brain tissues may contribute to the neuropathology of those neurological diseases but appear not to be a significant factor in other common disorders of the human brain and/or CNS.

Keywords advanced photon source (APS) · Aluminum · Alzheimer's disease (AD) · Down's syndrome (DS; trisomy 21) · electrothermal atomic absorption spectrophotometry (ETAAS) · Dialysis dementia syndrome (DDS) · prion disease (PrD) · temporal lobe neocortex · X-ray-fluorescence raster-scanning (XRFR) spectroscopy

Introduction

Environmentally abundant in our biosphere and highly neurotoxic, aluminum has been linked to the development of multiple neurological disorders of the human central nervous system (CNS). The progressive accumulation and compartmentalization of aluminum within the aging human CNS have been implicated in various neuropathological processes and disease mechanisms involving amyloidogenesis, pro-inflammatory signaling, innate-immune disruption, neural degeneration and alterations in the expression of brain-essential genetic information. These neurochemical and molecular genetic changes appear to be directly associated with deficits in behavior, cognition and memory in patients with aluminum-implicated neurological and/or neurodevelopmental conditions [1–15]. More specifically, aluminum, an extremely high charge density cation ($Z^2/r = 18$), appears to induce a general neurotoxicity towards both intracellular and extracellular signaling functions in the CNS wherever

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phosphates or polyphosphates are encountered, such as in the phosphate-rich genetic material that includes RNA, DNA, free nucleotides such as adenosine triphosphate (ATP), phosphoproteins and single stranded nucleic acids [3, 16–20]. More precisely, bioavailable aluminum appears to be responsible for a significant reactive oxygen species (ROS) mediated genotoxicity, that is, toxicity toward the genetic material of the cell and molecular-genetic operations that include transcription, intra- and extra-nuclear genetic signaling, epigenetics and gene-expression that has been extensively described by various laboratories [3, 7, 9, 10, 21–35]. Aluminum-induced genotoxicity appears to be mediated through (i) upregulation of the heterodimeric, pro-inflammatory transcription factor NF-kB (p50/p65) complex; (ii) significant increases in NF-kB-sensitive microRNA (miRNA) and messenger RNA (mRNA) linked signaling circuits; and (iii) deficits in gene expression within the CNS. These have been shown to drive multiple and highly interactive aspects of inflammatory neurodegeneration including amyloidogenesis, altered innate-immune responses, deficits in neurotrophic signaling and synaptogenesis, and the inability to clear self-aggregating waste material from the brain cell cytoplasm and parenchyma [5, 6, 10, 12, 29–38].

Our laboratories have a major ongoing research interest in environmental biochemistry and the neurotoxicity of biosphere-abundant neurotoxins. Aluminum is the 3rd most abundant element (after oxygen and silicon) and the most abundant metal making up about ~8.1% (w/v) of the entire earth's crust – the determination of the abundance of neurotoxic metals such as aluminum in human CNS tissues has been an ongoing operation in our laboratories for over 40 years. It is important to point out that even though aluminum may be more abundant in one neurological disease or tissue fraction than another, it is further important to demonstrate that aluminum at physiologically realistic concentrations is capable of contributing to an aluminum-driven neuropathology that is relevant to that particular CNS disease [6, 14, 22, 39–42]. For example, ambient aluminum sulfate at low nanomolar concentrations, as might be encountered within the genetic material of the aging CNS, has the ability to emulate the upregulated levels of the same microRNAs (miRNAs) as are apparent in AD, DS, some aged human brain tissue samples, and in several transgenic murine models of these neurodegenerative diseases [30, 31, 35, 42, 43]. Interestingly, the synergism of aluminum with other neurotoxic metals, such as environmental iron and mercury, in mediating and enhancing incapacitating neurotoxic effects within the human CNS is just beginning to become understood [27, 41].

Methods

At autopsy, human brain temporal lobe (Brodmann areas A20–A22) tissues were collected from deceased patients with a postmortem interval (PMI; death to brain freezing at − 81 °C) ranging from 1.2 to 5.0 h. Patient clinical, medial, and familial history, physical examination, clinical dementia rating (CDR), pneumoencephalogram and/or other neuropathological determinations were compatible with the diagnosis of each respective neurological disorder. To avoid gender-based neurochemical or neurophysiological bias, only female brains were utilized in this study with the exception of the ASD group consisting of 7 females and 19 males. Extensive postmortem examination revealing brain weight, brain atrophy, neurofibrillary degeneration, senile plaques, evidence of micro-bleeds and stroke, hippocampal pyramidal degeneration, and related clinical parameters was consistent with a diagnosis of each neurological disorder. Because of a massive data loss on 23–31 August 2005 due to hurricane Katrina, only the mean and standard deviation for the age of each neurological group studied was available. Great care was taken in the removal and processing of tissues, and workers in autopsy suites were supervised to minimize possible aluminum contamination; for aluminum determinations, brain tissues were typically handled and processed in a negative-pressure clean room area used for the manipulation of extremely labile single-stranded RNA molecules. Further details of the analytical methods for aluminum samples are given in Supplementary File 1. Using ETAAS, as little as 0.1 μg/g (dry weight) aluminum can be reliably detected; however, the ETAAS method measures the total amount of aluminum, and the possibility that this element is bound in a nontoxic or non-specific form or in a physiological situation that has no neurotoxic effect cannot be excluded at this time. Although a considerable amount of investigational work has been done by this laboratory on the genotoxic effects of aluminum on gene expression, it will be necessary to further identify and characterize the tissue-binding sites in AD, DDS, and DS to further establish the role of aluminum in the pathogenesis of each disease. For example, it has been shown that in AD, aluminum may target certain "open" or "euchromatic" regions of the brain and hence be compartmentalized to specific chromatin structures such as the internucleosomal "histone-H1" linker region, i.e., in highly compartmentalized fractions of the entire brain cell [40, 44]. In addition, not all of the pathological changes in AD, DDS, DS, and the other neurological conditions studied here can be readily explained by these findings, and our study does not exclude the possibility of other etiological factors including other neurotoxic processes, molecules, or environmental metals that may further contribute to the pathogenic mechanism of progressive inflammatory degeneration.

Results

Results for the aluminum content of temporal lobe tissues from 16 neurological disorders, a young control group (YCG), and an aged control group (ACG) are presented in Table 1 and

Table 1 summarizes the aluminum content of temporal lobe neocortical tissues from 16 neurological diseases, a young control group (YCG), and an aged control group (ACG) analyzed in this study. *N*, number of individual brains examined; *S.D.*, one standard deviation; *range*, lowest to highest aluminum signal quantified; the mean age (year) ± S.D. is the mean of the age of individual patients afflicted with each neurological disease plus one standard deviation of that mean; *$p < 0.0001$ ANOVA; *p*, significance; *ANOVA*, analysis of variance; *S*, significant; *NS*, not significant; *NA*, not applicable

Abbreviation	Neurological disease	Al, μg/g dry weight						
		N	Mean	S. D.	Range	*p*, ANOVA	S or NS	Mean age (year) ± S.D.
AD	Alzheimer's disease	186	8.08	2.91	1.9–16.8	< 0.0001	S	73.1 ± 15.6
AFT	Ataxia-Friedreich's type	6	1.15	0.18	0.9–1.4	1	NS	69.3 ± 11.5
ALS	Amyotrophic lateral sclerosis	16	1.22	0.14	0.95–1.4	1	NS	67.5 ± 10.1
ASD	Autism spectrum disorder	26	1.22	0.2	0.9–1.6	1	NS	11.1 ± 6.4
DDS	Dialysis dementia syndrome	27	3.69	1.14	1.2–6.2	< 0.0001	S	72.4 ± 13.2
DS	Down's syndrome (trisomy 21)	24	4.53	1.18	2.0–7.1	< 0.0001	S	75.3 ± 9.3
HC	Huntington's chorea	15	1.69	0.9	0.3–3.1	1	NS	70.4 ± 14.3
MID	Multiple infarct dementia	19	1.35	0.31	1.0–2.1	1	NS	70.4 ± 10.3
MS	Multiple sclerosis	23	1.37	0.43	0.7–2.1	1	NS	71.5 ± 9.3
PD	Parkinson's disease	27	1.77	0.76	0.4–3.2	0.9998	NS	72.5 ± 10.1
PrD	Prion disease (BSE, CJD, GSS)	11	1.31	0.34	0.9–2.1	1	NS	74.2 ± 9.8
PML	Progressive multifocal leukoencephalopathy	11	1.5	0.56	0.7–2.3	1	NS	73.1 ± 16.3
PSP	Progressive supranuclear palsy	24	1.45	0.4	0.5–2.3	1	NS	71.9 ± 14.4
SCZ	Schizophrenia	21	1.74	0.56	0.9–1.5	1	NS	69.3 ± 11.6
YCG	Young control group	22	1.2	1.19	0.9–1.5	NA	NA	10.2 ± 6.1
ACG	Aged control group	53	1.34	1.34	0.16–1.8	NA	NA	71.4 ± 9.3

Figure 1; raw data for each neurological disorder is presented in Supplementary File 2. The neurological disorders AFT, ALS, ASD, HC, MID, MS, PD, PrD, PML, PSP, and SCZ, while all representing neurological disorders with a neuroinflammatory and/or neurodegenerative component that include progressive memory, behavioral, or cognitive deficits did not show any significant increase in aluminum in the medial superior temporal lobes (Brodmann A20–A22) when compared to age-matched controls (Table 1). We note that the only neurological conditions exhibiting increased aluminum versus age- and gender-matched-healthy, neurologically normal controls were AD to a mean of ~ 8.08-fold over age- and gender-matched controls

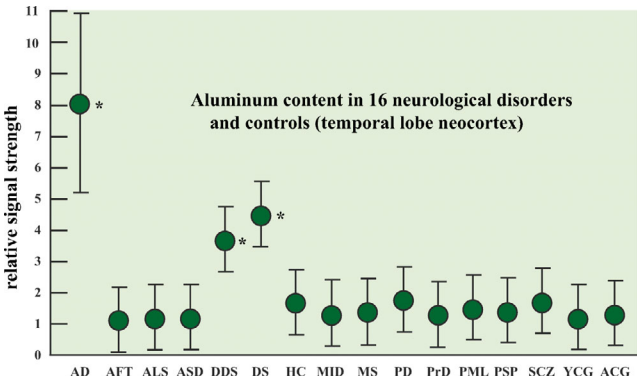

Fig. 1 Graphical depiction of the data in Table 1; *$p = 0.0001$ (ANOVA) and is highly significant'; N = 511

(*N* = 186; range, 1.9–16.8 μg aluminum/g tissue); DS (trisomy 21) to a mean of ~ 4.53-fold over age- and gender-matched controls (*N* = 24; range, 2.0–7.1 μg aluminum/g tissue); and DDS to a mean of ~ 3.69-fold over age- and gender-matched controls (*N* = 27; range, 1.2–6.2 μg aluminum/g tissue). These values are within the range of previously determined tissue aluminum studies using ETAAS [25, 45]. Of all brains studied, the highest aluminum concentrations were consistently found in AD tissues. Interestingly, all DS patients are known to expire from AD-type pathological change in their brains, and at postmortem examination, all DS patients exhibit some form of AD-type alterations in the brain parenchyma and/or the extraneuronal or extracellular space. These include prominently, the appearance of highly pro-inflammatory lesions including amyloid-beta (Aβ) peptide–enriched senile plaque deposits, and neurofibrillary tangles [15, 45–47]. The loss of normal kidney function in aged, long-term DDS patients exposes the entire circulatory system, including the cerebral vascular circulation, and potentially CNS compartments, to very large amounts of aluminum, usually in the form of aluminum-containing compounds in the dialysis fluids resulting in aluminum intoxication, marked by significant motor, speech and cognitive disturbances, seizures, and progressive dementia [18, 19, 25, 48, 49].

The latest US federal government compiled medical and scientific data, including updated disease information with demographic statistics on facts concerning AD, AFT, ALS, ASD, DDS, DS, HC, MID, PD, PML, PSP, SCZ, and PrP

(that includes BSE (mad cow disease), CJD, and GSS), provided by the National Institutes of Health, Bethesda, MD, USA, and other resources and constant updates are provided in Supplementary File 3.

Results employing other novel and experimental analytical techniques for aluminum quantitation and other trace metal-analysis using X-ray fluorescence raster scanning (XRFR) spectroscopy to advance and improve the analysis and resolution of aluminum abundance and speciation in neurobiological tissues are presented in poster format in Supplementary File 4 [50, unpublished data]. While still in development, using the APS XRFR spectroscopy device, for each sample, data were acquired using an energy dispersive germanium detector capable of detecting Al, P, S, Cl, K, Ca, Fe, and Zn non-destructively in complex biological samples. We have been able to detect a significantly larger signal for aluminum abundance in AD temporal lobe neocortex ranging from 6- to 9-fold over age- and gender-matched healthy controls, and the results are highly significant ($p < 0.0001$, ANOVA). In this ongoing project, our long-term goal is to advance our ability to analyze and quantify aluminum and other metal abundance, speciation, and complexity in extremely small samples of neurobiological tissues (Supplementary File 4).

Discussion

The biophysical, biomolecular, cellular, nuclear, genetic, epigenetic, and systemic mechanisms by which aluminum exerts selective neurotoxicity and genotoxicity remain incompletely understood. Many different pathogenic signaling pathways mediated by aluminum toxicity have been described by our group and others [3, 5, 10, 11, 19, 27, 31, 38, 47]. One major aluminum-induced pathogenic signaling pathway driving aluminum genotoxicity with relevance to many different human diseases has been discovered in which (i) aluminum crosses aging, diseased, or dysfunctional biophysical barriers including the gastrointestinal (GI) and blood-brain barriers (BBB); (ii) accesses aluminum sensitive compartments within the CNS and supports the generation of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS); (iii) these highly reactive species in turn strongly induces phosphorylation of the NF-kB inhibitor (IkB), thereby leading to the activation of the heterotypic NF-kB (p50/p65) dimer; (iv) NF-kB sensitive microRNAs (such as miRNA 34a and miRNA 146a) are significantly induced (due to the presence of multiple NF-kB DNA binding sites in the miRNA 34a and miRNA 146a gene promoters); and (v) these NF-kB sensitive miRNAs next interact with the 3′-untranslated region (3′-UTR) of target messenger RNAs (mRNAs), thereby leading to their degradation and decreasing the expression of that target mRNA [2, 13, 15, 30–32, 36, 51].

Therefore, a highly selected and pathogenic group of up-regulated, NF-kB sensitive, miRNAs ultimately causes, for example, the downregulation of several key brain essential mRNAs including those involved in synaptogenesis, in the regulation of innate immunity, inflammatory and neurotrophic signaling, and in amyloidogenesis [15, 42, 43]. Interestingly, it has recently been shown that human microbiome-derived lipopolysaccharide (LPS), and more specifically the LPS of the Gram-negative obligate anaerobe *Bacteroides fragilis* (BF-LPS), strongly adsorbs aluminum and is highly capable of inducing both ROS and RNS and NF-kB and inducing-inflammatory neurodegeneration in human brain cells in primary culture, thus establishing for the first time a link between potent aluminum containing, pro-inflammatory neurotoxins actively secreted by the GI tract microbiome and inflammatory signaling within human brain cells [52, 53, unpublished observations].

Along with ETAAS and XRFR, other experimental, investigative, and analytical methodologies for quantifying the abundance of aluminum in CNS tissues include high-field 19.6T ^{27}Al solid-state MAS NMR technologies which are designed to improve the detection and localization of aluminum in neurobiological tissue samples [54, 55]. These tissues include those of the normally aging human CNS, those with the neurological diseases referred to in this report, transgenic murine models of these same neurological disorders, and the use of primary human neuronal-glial (HNG) cell models co-cultured in vitro [27, 52, 54, unpublished 2018]. Related to aluminum localization and quantitative analytical work, other techniques such as “molecular shuttle chelation,” involving the use of ascorbate, desferrioxamine, and Feralex-G in combination to remove nuclear-bound aluminum have been advanced, although once bound, aluminum is particularly refractory to chelation-based removal, especially in the phosphate-enriched environment of euchromatin and the transcriptionally active micro-compartments of human brain cell nuclei [12, 14, 17, 35]. Interestingly, the only clinical trial specifically designed to remove aluminum from the brains of live control and AD patients (N=48) using the trivalent metal chelator desferrioxamine (DF) resulted in halving of the rate of neurodegeneration and cognitive decline in the DF-treated group [56, 57].

In conclusion, like all similar analytical studies on the role of environmentally-derived neurotoxins in age-related human neurological disease, these investigations have important limitations. We focused on aluminum content in females largely due to brain tissue sample obtainability; however, parallel exploratory studies, for example, in aged males with AD, also exhibit a consistent trend for aluminum accumulation in the temporal lobe and limbic regions of the brain versus healthy aging controls exhibiting no neurological disease. Tissue accessibility and sampling size from particularly rare neurological diseases such as ataxia Friedreich’s type (AFT), prion disease (PrD; including

BSE; "mad cow disease," CJD, and GSS), and progressive multifocal leukoencephalopathy (PML) are intrinsically problematic because (i) there is variability in neurotoxic metal concentrations among individuals; (ii) variations in the actual process of tissue acquisition, extraction, and processing; and (iii) small sample size and skewed power analysis could induce bias in both statistical analysis and overall interpretation of the results. Indeed, the enrichment of aluminum, or in fact any toxic metal, in tissues diagnosed with a specific neurological disorder, while certainly suggestive, should not alone be enough evidence to link that metal to any disease. Only careful experimental design and reproducible experimentation with appropriate controls are required to show that any neurotoxic metal is capable of causing a focused disruption of a neurological process. Importantly, this neurotoxic metal disturbance should have a direct relevance to the neurological disease process itself and occur at realistic concentrations equivalent to those found under pathophysiological conditions *in vivo* [1–5, 7–9, 31, 32, 40, 56, 57].

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Authors Contributions DRCM, CB, PNA, WW, AIP, MEP, TPAK, YZ, NS,VJ, and WJL aided in the acquisition of all brain tissues and performed all analytical experiments involving ETAAS and XRFR and assisted to interpret and analyze all data; PNA, ZF, AIP, YZ, WL and WJL collected, archived, organized, and tabulated all data and performed statistical analysis; AIP and WJL wrote the paper.

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Compliance with Ethical Standards

Ethics Statement All acquisition, handling, experimental, and analytical procedures involving postmortem human brain tissues were carried out in an ethical manner in strict accordance with the ethics review board policies at brain and tissue donor institutions and at the Louisiana State University (LSU) Health Sciences Center. Informed consent from next of kin was obtained at brain and tissue donor institutions for all tissue samples prior to autopsy and donation; coded postmortem brain tissue samples (containing no personal identifying information of the donors) were obtained from the 18 brain and tissue banks listed in the Acknowledgements section above. The ethical use of postmortem human brain tissues and their analyses were also carried out in strict accordance with the Institutional Biosafety Committee and the Institutional Review Board Committee (IBC/IRBC) ethical guidelines IBC#18059 and IRBC#6774 at the LSU Health Sciences Center, New Orleans LA 70112 USA.

Conflict of Interest Statement Declaration of interest for all authors including financial and personal relationships with other people or organizations: none. We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. The experimental and research work in this paper was funded by the LSU Eye Center from Research to Prevent Blindness (RPB), the Louisiana Biotechnology Research Network (LBRN), the National Institutes of Health (NIH), Bethesda MD, USA and the Alzheimer Association Chicago IL, USA,

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